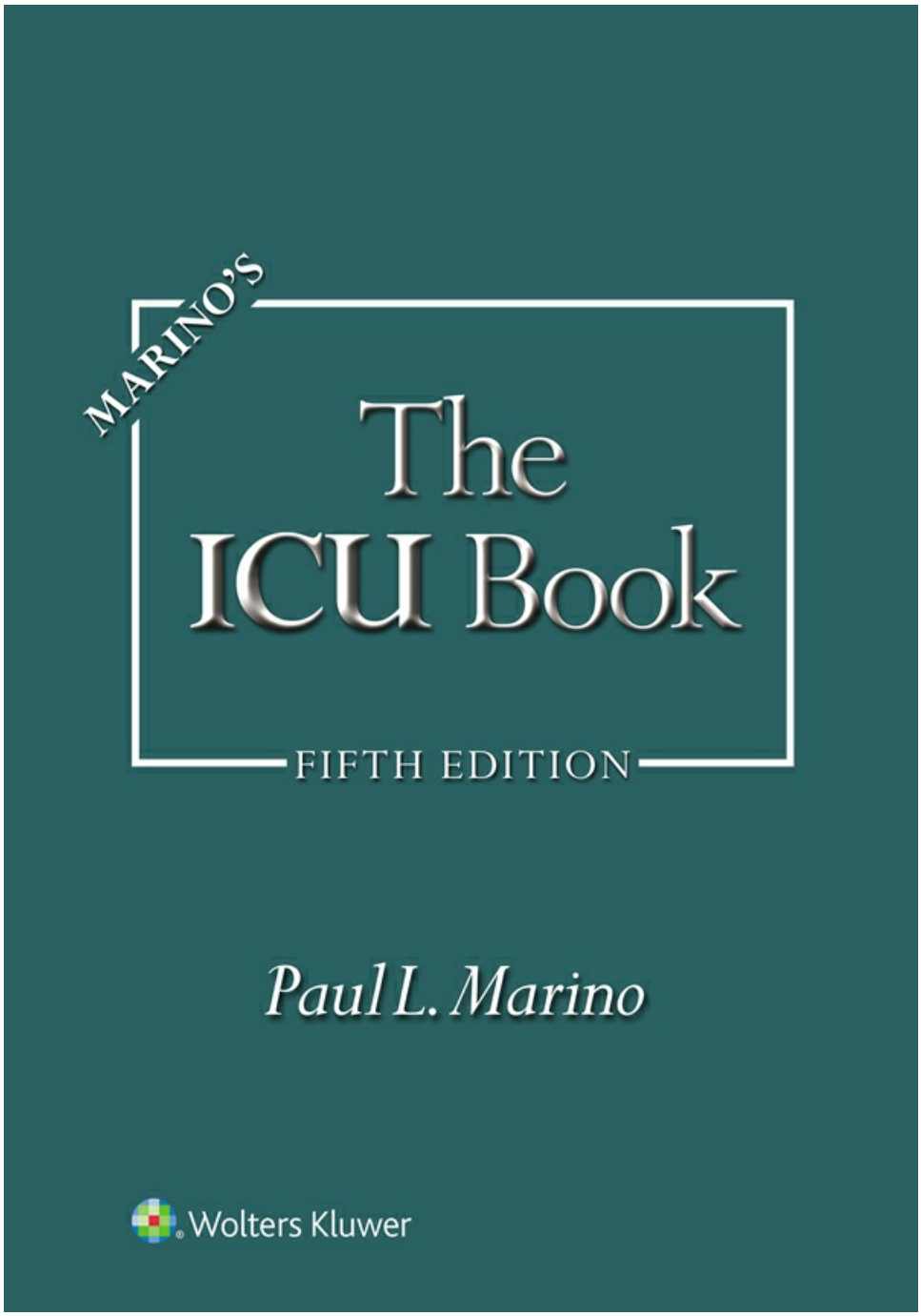
MARINO'S

The ICU Book

FIFTH EDITION

Paul L. Marino

Wolters Kluwer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To my son,
Daniel Joseph Marino,
who is well into manhood,
but I can still see the little boy.

I would especially commend the physician who,
in acute diseases, by which the bulk of mankind
are cut off, conducts the treatment better than others.

HIPPOCRATES

Preface to Fifth Edition

The fifth edition of The ICU Book marks its 33rd year as a fundamental sourcebook for the care of critically ill adults. This edition continues the original intent to craft a textbook that focuses on fundamental concepts and practices that can be used in any ICU, regardless of the specialty designation of the unit. Creating succinct presentations that are easy to understand has always been a priority, and has been a popular feature of past editions.

This edition has been reorganized and completely rewritten, with updated references and clinical practice guidelines included at the end of each chapter. There are 53 chapters (two fewer than the fourth edition), with new chapters on Fluid Management (Chapter 11), Approaches to Clinical Shock (Chapter 14), Cardiogenic Shock (Chapter 16), Acute Pulmonary Embolism (Chapter 22), and Noninvasive Ventilation (Chapter 26). (Consolidation of the material in several chapters in the fourth edition has allowed for the addition of new chapters without increasing the total length of the book.) The text is supplemented with 238 original illustrations and 207 tables (an average of 4–5 illustrations and 4 tables per chapter) and each chapter ends with a brief section titled “A Final Word”, where the author provides some insight about a relevant issue, or highlights some pertinent points in the chapter.

The ICU Book is unique in that it is the educational contribution of a single author, who has now accumulated 44 years of experience as a critical care specialist. The hope is that this contribution incites perceptions similar to those in the following quote (which is from the Foreword to another single-authored medical textbook) (1):

> “What a rarity! A single-authored medical text, regularly updated, the essence needed by newcomers and old-timers alike, extracted from the world’s literature without assistance, barely increasing its bulk, while keeping it clear, concise, and comprehensive.”

1. Severinghaus JW. Foreword. In: Nunn *JF. Nunn’s Applied Respiratory Physiology*, 4th ed. Oxford: Butterworth-Heinemann Ltd, 1993.

Acknowledgments

Acknowledgments are few but well deserved. First to Keith Donnellan, my editor and my friend, whose affable nature is matched only by the mastery of his craft. And to Patricia Gast, my longtime associate and ‘right arm’, who is responsible for the illustrations, tables, and page layouts in this book. This is our 6th book together, and none of them would have been possible without her. And finally, to the online library service of Weill Cornell Medical College, which provides ready access to innumerable English-language medical journals (a must for any author of a medical text).

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Section I

VASCULAR ACCESS

He who works with his hands is a laborer.
He who works with his head and his hands is a craftsman.

Louis Nizer
Between You and Me
1948

Chapter 1

Vascular Access Primer

It is not a bad definition of man to describe him as a tool-making animal.

Charles Babbage (*a*)

INTRODUCTION

One of the most dramatic events in medical self-experimentation took place in a small German hospital during the summer of 1929, when an intrepid surgical resident named Werner Forssmann inserted a plastic urethral catheter into the basilic vein in his right arm and advanced the catheter into the right atrium of his heart (1). This was the first documented instance of a right-heart catheterization in a human subject, but Dr. Forssmann received no accolades, as he had acted in defiance of the senior surgical staff at his hospital. Instead, he was promptly dismissed from his residency for actions that were perceived as inappropriate and reckless. Upon dismissal, he was told that "such methods are good for a circus, but not for a respected hospital" (1). Dr. Forssmann went on to become a country doctor, but his achievement in vascular cannulation was finally recognized in 1956, when he was awarded the Nobel Prize in Medicine.

Werner Forssmann's achievement was possible because he used a flexible plastic catheter that could safely follow the contours of the venous system as it was advanced. This was a departure from the traditional practice of cannulating blood vessels with rigid needles and metal cannulas, and it heralded the modern era of vascular cannulation, which employs a wide array of flexible plastic catheters like the ones described in this chapter.

CATHETER BASICS

Vascular catheters are made of synthetic plastic polymers that are chemically inert, biocompatible, and resistant to chemical and thermal degradation. Catheters that are used for short-term cannulation (days to weeks) are typically made of *polyurethane*, a versatile polymer that is pliable, yet provides enough tensile strength to resist kinking during catheter insertion. (The elastic fibers used in stretchable clothing are made of polyurethane.) Catheters that are used

for long-term vascular access (months) are typically made of *silicone*, which is much more pliable than polyurethane (e.g., the nipple on baby bottles is made of silicone) and is less likely to cause vascular damage. Because of their pliability, silicone catheters are difficult to insert percutaneously, and are used primarily as implantable catheters (such as those used for long-term chemotherapy).

Catheter Size

The size of vascular catheters is a reflection of the *outside diameter* of the catheter. There are two expressions of catheter size: gauge size and French size. The correlation between the two is shown in Table 1.1.

Gauge Size

The gauge system was introduced (in England) for sizing solid iron wires, and was later adopted for hollow needles and catheters. Gauge size is a measure of how many wires (or catheters) can be placed side-by-side in a given space, and it varies inversely with outside diameter (OD); i.e., the higher the gauge size, the more catheters will fit in a given space, and thus the smaller the OD. Unfortunately, the actual OD for each gauge size is not standardized, and varies with each manufacturer. Gauge sizes are typically used for needles, small-bore single-lumen catheters, and the infusion channels in multilumen catheters; sizes typically range from 16 gauge (largest diameter) to 21 gauge (smallest diameter).

French Size

The French system was introduced (guess where) for sizing hollow tubes (catheters), and it provides a more predictable measure than the gauge system. The French scale begins at zero, and each increment of one French unit represents an increase in OD of 0.33 millimeters (2): i.e.,

$$\text{French size (Fr)} \times 0.33 = \text{OD (mm)}. \tag{1.1}$$

French sizes are used for multilumen catheters and large-bore single-lumen catheters; sizes typically range from 4 Fr (1.2 mm OD) to 9 Fr (3.2 mm OD). French sizing is also used for urinary catheters, nasogastric tubes, and pleural drainage tubes.

Flow Through Catheters

The determinants of flow through narrow, rigid tubes (e.g., catheters) was first described by a German civil engineer (Gotthilf Hagen) and a French physician (Jean Marie Poiseuille), working independently in the mid-19th century. Their observations are expressed in the following equation, known as the *Hagen-Poiseuille equation* (3).

$$Q = \Delta P \times (\pi r^4/8\mu L). \tag{1.2}$$

This equation states that the steady or laminar flow rate (Q) in a rigid tube is directly related to the pressure gradient along the tube ($\Delta P = Pin - Pout$) and the fourth power of the radius of the tube (r^4), and is inversely related to the length of the tube (L) and the viscosity of the fluid (μ). The term enclosed in parentheses is equivalent to the reciprocal of resistance (according to the relationship: $Q = \Delta P \times 1/R$), so the resistance to flow can be expressed as: $R = 8\mu L/\pi r^4$.

TABLE 1.1	Correlation between French and Gauge Sizes	
French Size	**Gauge Size**	**Outside Diameter**
1	27	0.4 mm
3	20	0.9 mm
4	18	1.2 mm
5	16	1.7 mm
7	13	2.4 mm
9	11	3.2 mm

From Access Technologies, 2016 catalogue (available at www.norfolkaccess.com).

Catheter Dimensions

The Hagen-Poiseuille equation describes the influence of catheter dimensions on flow through the catheter. This is an important consideration because *the infusion rate of intravenous fluids is determined by the dimensions of the indwelling catheter, and not by the size of the cannulated vein*. The inner radius of the catheter has a profound influence on flow (because flow rate is directly related to the fourth power of the radius), and this is demonstrated in the bar graph on the left in Figure 1.1 (4). In this case, the gravity-driven flow of water through a 16 gauge catheter was more than double the flow through an 18 gauge catheter, and was almost four times greater than the flow through a 20 gauge catheter (with all catheters being equal in length). The large difference in flow rates between 16 and 20 gauge catheters is associated with less than a one millimeter difference in outside diameter (see Table 1.1), which highlights the importance of catheter diameter as a determinant of flow.

The Hagen-Poiseuille equation also shows that flow will vary in an opposite direction to changes in the length of a catheter; this is demonstrated in the graph on the right in Figure 1.1 (5). Note that the transition from a two-inch catheter (a common length for peripheral vein catheters) to a six-inch catheter (a common length for central venous catheters) is associated with a 40% reduction in flow, and a further transition to a 12-inch catheter (an available length for central venous catheters) is associated with an additional 40% decline in flow.

The information just presented indicates that *when rapid volume infusion is needed, a large-bore catheter is the appropriate choice, and a short, large-bore catheter is the optimal choice.*

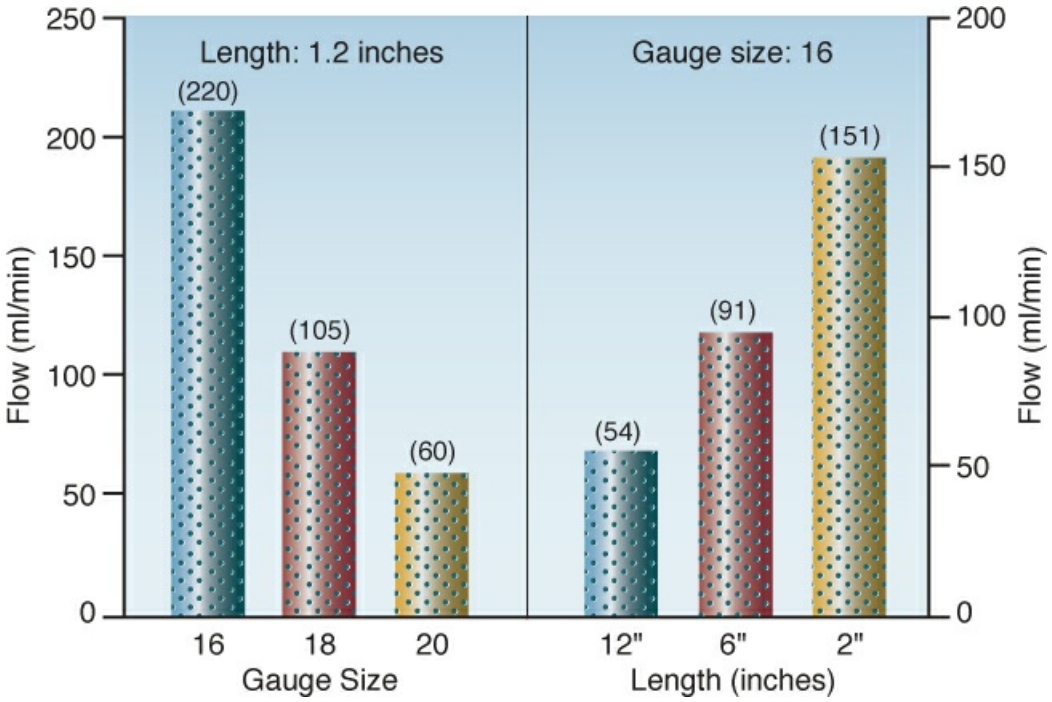

FIGURE 1.1 Graphs demonstrating the influence of catheter diameter (panel on the left) and catheter length (panel on the right) on flow rate. See text for further explanation. Data from References 4 and 5.

Infusion Pressure

The resistance to flow created by vascular catheters can be overcome by increasing the pressure gradient for flow (i.e., the ΔP in Equation 1.2). In a gravity-driven infusion system, this is accomplished by increasing the height of the infusate container (bag or bottle) above the cannulation site: e.g., a height of 68 cm (27 inches) will create an infusion pressure of 50 mm Hg (or one pound per square inch, psi), and an increase in height to 100 cm (39 inches) will increase the infusion pressure to 75 mm Hg (1.5 psi) (6).

INFUSION PUMPS: Intravenous fluids and drugs are typically delivered at specific infusion (or dose) rates, and this control is achieved with programmable infusion pumps that adjust the infusion pressure (up to 15 psi) to deliver a preselected infusion (or dosage) rate. There are two types of infusions pumps: *volumetric pumps*, which can deliver one liter of fluid (from a bag or bottle) at flow rates of 0.1 to 1,000 mL/hr, and *syringe drivers* that operate with a lower volume (up to 100 mL) and deliver fluid at rates of 0.1 to 100 mL/hr (6). *Volumetric pumps* are general-purpose devices that are used to deliver intravenous fluids and most intravenous drugs, while syringe pumps are popular for patient-controlled analgesia. There are also specialized infusion pumps for the resuscitation of massive hemorrhage. These devices deliver warmed fluids or blood products at rates of up to 1.5 L/min when combined with specialized “rapid infusion catheters” that are typically 7–8 French in diameter and 2–2.5 inches in length.

GENERAL-PURPOSE CATHETERS

Intravenous catheters are classified as central or peripheral catheters based on the following simple distinction: central catheters extend into one of the vena cavae, and peripheral catheters do not. The following is a description of the peripheral and central catheters that are used in everyday patient care in the ICU. Catheters with a specialized function, like hemodialysis catheters and pulmonary artery catheters, are described elsewhere in the book. (Chapter 8 is devoted entirely to the pulmonary artery catheter.)

Peripheral Catheters

Peripheral catheters are typically inserted into one of the veins in the upper extremity, and they do not extend beyond the shoulder. Three distinct types of peripheral catheter have been identified (7,8): short peripheral catheters (<6 cm in length), long peripheral catheters (6 to <15 cm in length), and midline catheters (15 to 20 cm in length).

Short Peripheral Catheters

The traditional method of cannulating peripheral veins involves a 16–22 gauge catheter that is 3–5 cm (1–2 in) in length, and is placed in a visible or palpable vein (usually in the upper extremity) using a catheter-over-needle device like the one in Figure 1.2. The tip of the catheter is recessed back from the tip of the introducer needle, and is tapered to prevent fraying as the catheter is advanced into the blood vessel. When the tip of the probe needle enters the vein, a "flashback" of blood appears in the clear hub of the needle. When this occurs, the catheter is advanced over the needle and into the lumen of the blood vessel.

Cannulation with short peripheral catheters is favored because it provides rapid vascular access (when a superficial vein is visible or palpable), although the initial cannulation attempt fails in about one-third of cases (9). The major disadvantage of short catheters is their limited "dwell time" (the time an indwelling catheter remains functional); the reported failure rate of these catheters is 40–60% within the first 3 days (8). Common causes of failure include localized phlebitis, catheter occlusion or dislodgement, and vascular perforation with extravasation of infused fluids. Short peripheral catheters are especially problematic in ICU patients, who are often agitated and prone to dislodging these catheters.

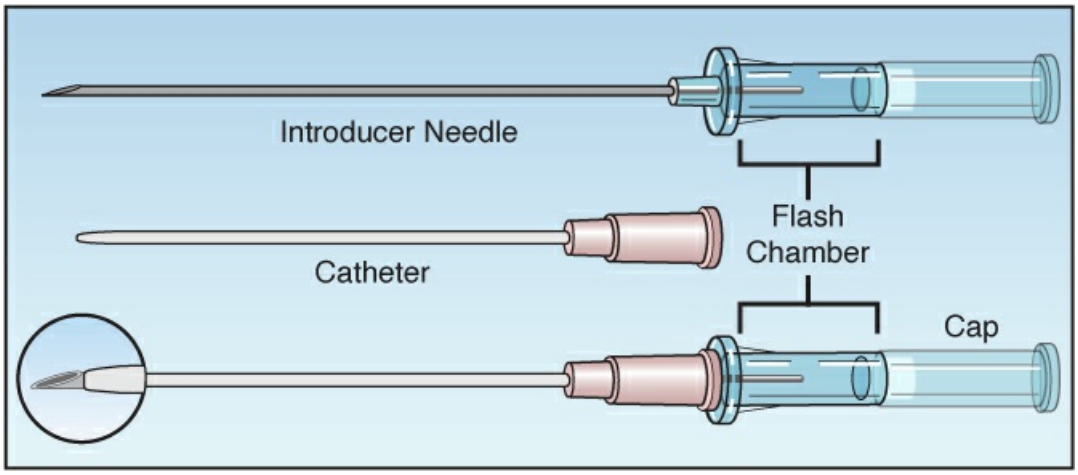

FIGURE 1.2 A catheter-over-needle device used to cannulate superficial peripheral veins.

Long Peripheral Catheters

Long peripheral catheters (also known as “extended dwell catheters”) are typically 8 cm (3.1 inches) in length, and were introduced to improve the stability and dwell time of the short peripheral catheters. Clinical studies have consistently shown a longer dwell time with the longer catheters (about 7–9 days) (10). Despite this advantage, long peripheral catheters have not been embraced (at least not in North America), possibly due to the growing popularity of midline catheters (see next).

Midline Catheters

Midline catheters are the longest of the peripheral vein catheters (15–20 cm in length), and are inserted into one of three deep veins above the antecubital fossa: the basilic, brachial, or cephalic veins (see Figure 1.3). The basilic vein is preferred because it runs a direct course up the arm, and is not in close proximity to an artery or nerve (like the brachial vein). Because the major veins in the upper arm are deeply situated ultrasound guidance is used for midline catheter insertion (see later for a description of ultrasound guided cannulation). When properly placed and maintained, midline catheters can remain functional for weeks; e.g., in one clinical study, the average dwell time for midline catheters was 14 days (11). This same study also demonstrates that *vasopressors can be infused through midline catheters for as long as 7–8 days* without evidence of extravasation or limb compromise (11).

The extended dwell time of midline catheters have made them a popular choice when more than a few days of venous access is anticipated. In fact, midline catheters are now considered a safer alternative to the much longer “peripherally inserted central catheters” or PICCS (described in the next section), which have traditionally been favored for prolonged venous access. Comparative studies have shown that midline catheters have a lower incidence of catheter occlusions and catheter-related bloodstream infections than PICCs (12). Although there is a slightly higher risk of deep vein thrombosis (DVT) with midline catheters, the incidence of DVT with midline catheters is low (<5%), and the difference between midlines and PICCs is small (<2%) (13).

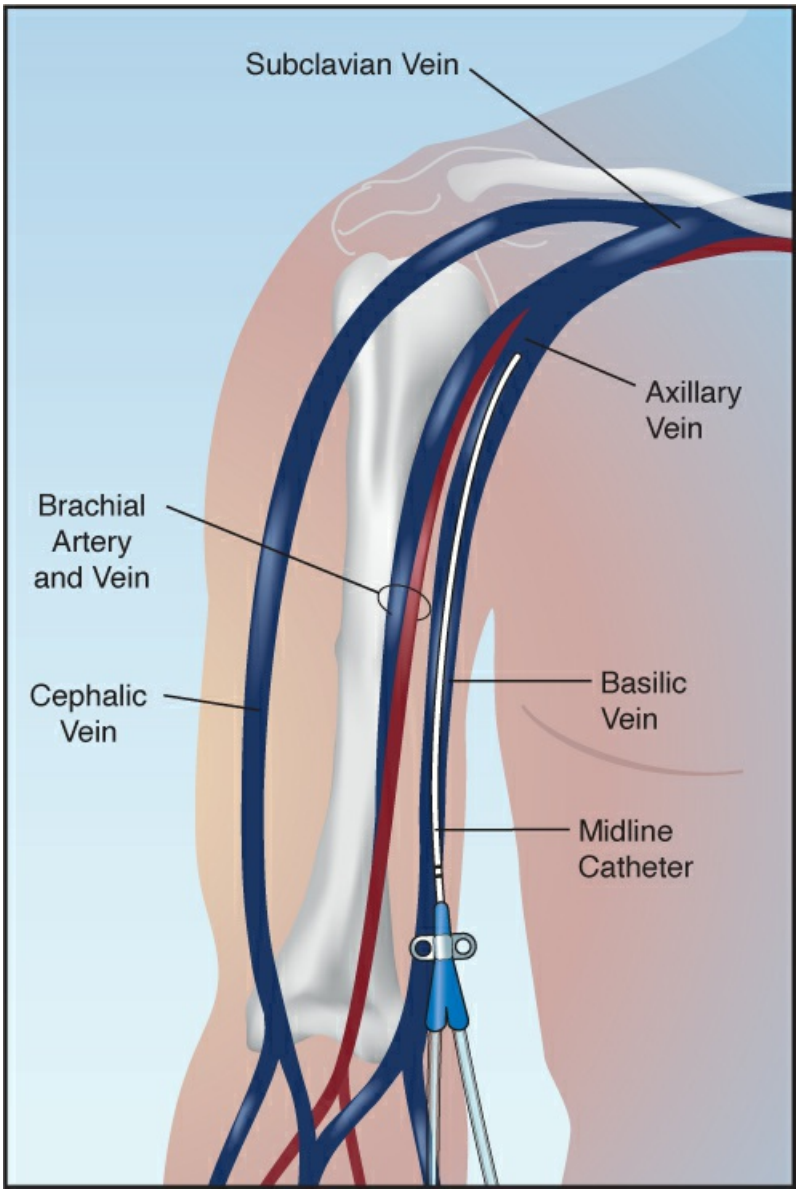

FIGURE 1.3 Illustration depicting the major veins un the upper arm, with a midline catheter in the basilic vein (the favored vein for midline catheter insertion).

TABLE 1.2 Comparative Features of Selected Peripheral Catheters

Catheter	Size	Length	Flow (L/hr)†
Short Peripheral Catheter[1]	18 ga	3 cm 1.2 in	6.0
Long Peripheral Catheter[2]	18 ga	8 cm 3.1 in	3.7
Double Lumen Midline Catheter[2]	Size: 5.5 French Lumens: 18 ga	15 cm 6 in	1.3/lumen

†All flow rates are for the gravity-driven flow of water from a height of 40 inches.

[1]Data from www.emupdates.com (accessed 5/17/2022).

[2]Data for Arrow® catheters, from www.teleflexvascular.com (accessed 5/17/ 2022). ga = gauge size, Fr = French

size.

Midline catheters are available in lengths of 15 cm and 20 cm, and can have one to three infusion channels. The double-lumen catheter that is 15 cm in length is a popular choice, and some features of this catheter are included in Table 1.2. Note that the increased length of the midline catheter is accompanied by a decrease in flow capacity; in this case, the gravity-driven flow rate in each lumen of the midline catheter is only about 20% of the flow rate in the short peripheral catheter. Despite this flow decrement, the gravity-driven flow capacity in the midline catheter still exceeds the maximum flow provided by volumetric infusion pumps (i.e., 1 L/hr).

Central Catheters

As mentioned earlier, central vein catheters have a tip in one of the vena cavae. There are two types of central catheters, based on the location of the insertion site: *peripherally inserted central catheters* (PICCs) are inserted into one of the veins in the upper arm, while *centrally inserted central catheters* (commonly known as *central venous catheters*) are inserted into one of the major veins near the thoracic inlet, or in the groin.

Peripherally Inserted Central Catheters

Peripherally inserted central catheters (PICCs) are essentially a longer version of the midline catheters: i.e., they are inserted via the same veins as the midline catheters, but are long enough to be advanced into the superior vena cava. These catheters have been popularized as a safer alternative to central venous catheters when peripheral vein cannulation is problematic, or when more than one week of vascular access is anticipated (14). However, the emergence of midline catheters as a safer alternative to PICCs has led to a steady decline in the popularity of PICCs in hospitalized patients.

PICCs are available in lengths ranging from 40 cm to 55 cm, and can have one to three infusion channels. A popular choice is the double-lumen PICC that is 50 cm in length, and some features of this catheter are shown in Table 1.3. Note that the extended length of the PICC results in a marked decrease in flow capacity: e.g., the PICC in Table 1.3 is more than three times the length of the midline catheter in Table 1.2, and the resulting flow capacity is only 20% of that in the midline catheter. The compromised flow capacity in PICCs may explain the relatively high incidence of occlusions in these catheters (12).

Central Venous Catheters

Central venous catheters (CVCs) have played a prominent role in providing both secure and multifunctional venous access in critically ill patients. (The insertion of CVCs is described in detail in the next chapter.) These catheters are available in lengths of 15 cm, 20 cm, and 30 cm, and can have as many as 4 infusion channels. The most popular CVC is a triple-lumen catheter like the one shown in Figure 1.4. Note that the distal lumen has a larger bore (16 gauge) than the proximal or medial lumens (18 gauge); as a result, the flow capacity in the distal lumen is more than double that in the other lumens, as indicated in Table 1.3. For this reason, the distal lumen of a CVC is best suited for rapid volume infusions.

TABLE 1.3 Comparative Features of Selected Central Catheters

Catheter	Size	Length	Lumens	Flow (L/hr)†
Triple Lumen CVC	7 Fr	20 cm (8 in)	Distal (16 ga) Medial (18 ga) Proximal (18 ga)	2.28 0.91 0.99
Double Lumen PICC	5.5 Fr	50 cm (20 in)	Distal (18 ga) Proximal (18 ga)	0.26 0.27

†All flows rates are for the gravity-driven flow of water from a height of 40 inches.

Data for Arrow® catheters, from teleflexvascular.com (accessed 5/18/2022).

CVC = central venous catheter,

PICC = peripherally inserted central catheter, ga = gauge size, Fr = French size.

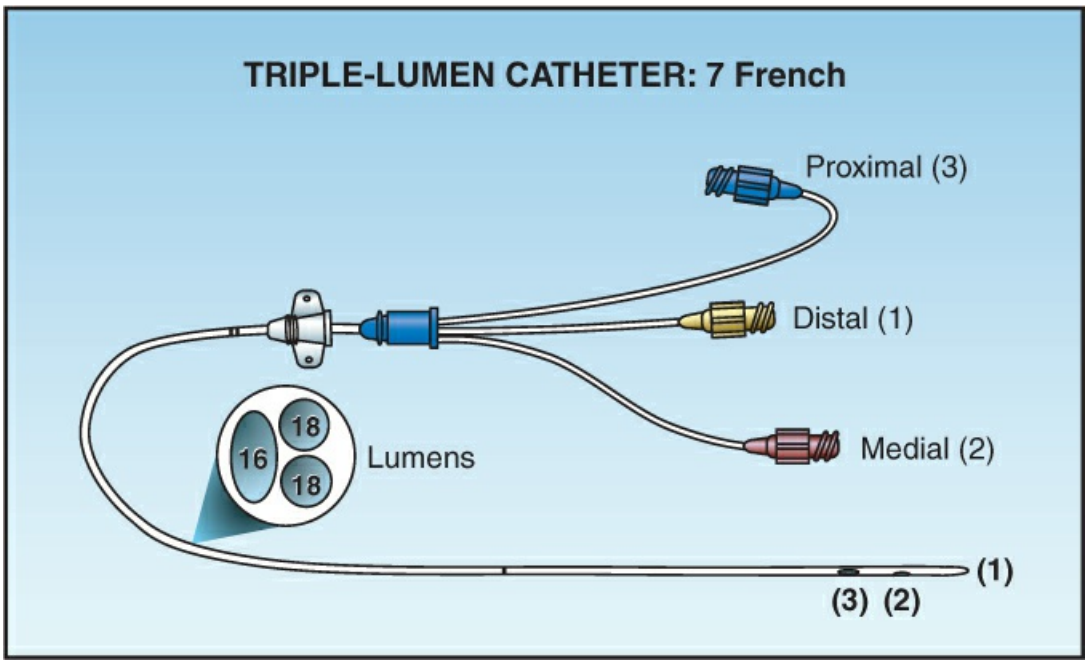

FIGURE 1.4 A triple-lumen central venous catheter, showing the gauge size of each lumen and the position of the outflow ports at the distal end of the catheter. This is currently the most popular design for central venous catheters.

The insertion of CVCs has been a staple of patient care in ICUs, but the popularity of CVCs is waning, as safer alternatives (i.e., PICCs and midline catheters) have emerged. (For more on the insertion of CVCs, see Chapter 2.)

The Guidewire

Cannulation of all but the most superficial, palpable veins is accomplished by advancing the catheter over a guidewire that is placed in the lumen of the vein. This technique of guidewire-assisted vascular cannulation, first introduced by a Swedish angiographer named Sven-Ibar Seldinger (and known as the *Seldinger technique*) (15), is illustrated in Figure 1.5. A small bore needle is used to probe for the target vessel. When

the tip of the needle enters the vessel, a thin wire with a flexible tip is passed through the needle and into lumen of the blood vessel. (The flexible tip reduces the risk of en dothelial injury as the guidewire is advanced.) The needle is then withdrawn over the guidewire, and the catheter is advanced over the guidewire and into the lumen of the blood vessel. (In actual practice, a “dilator catheter” is first threaded over the guidewire to create a tract that facilitates catheter insertion.)

Summation

The advantages and disadvantages of general-purpose vascular catheters are summarized in Table 1.4. The following is a brief summary of how these catheters are used for patient care in the ICU. Short peripheral catheters are preferred for quick intravenous (IV) access at the outset, but in patients who spend more than a few days in the ICU, more stable IV access is needed. This has been traditionally supplied by CVCs, but over the past decades, PICCs began to replace CVCs for longer-term IV access. More recently, midline catheters have emerged as an acceptable choice for longer-term IV access, and they are replacing CVCs and PICCS for this purpose. However, PICCS continue to be popular for patients who require extended (several weeks) IV therapy. The major drawback of midline catheters and PICCs is the use of specially trained teams to insert the catheters; this limits the availability of these catheters.

Central venous catheters are the final (go-to) catheters for stable venous access, and are especially preferred in patients with life-threatening hemodynamic instability.

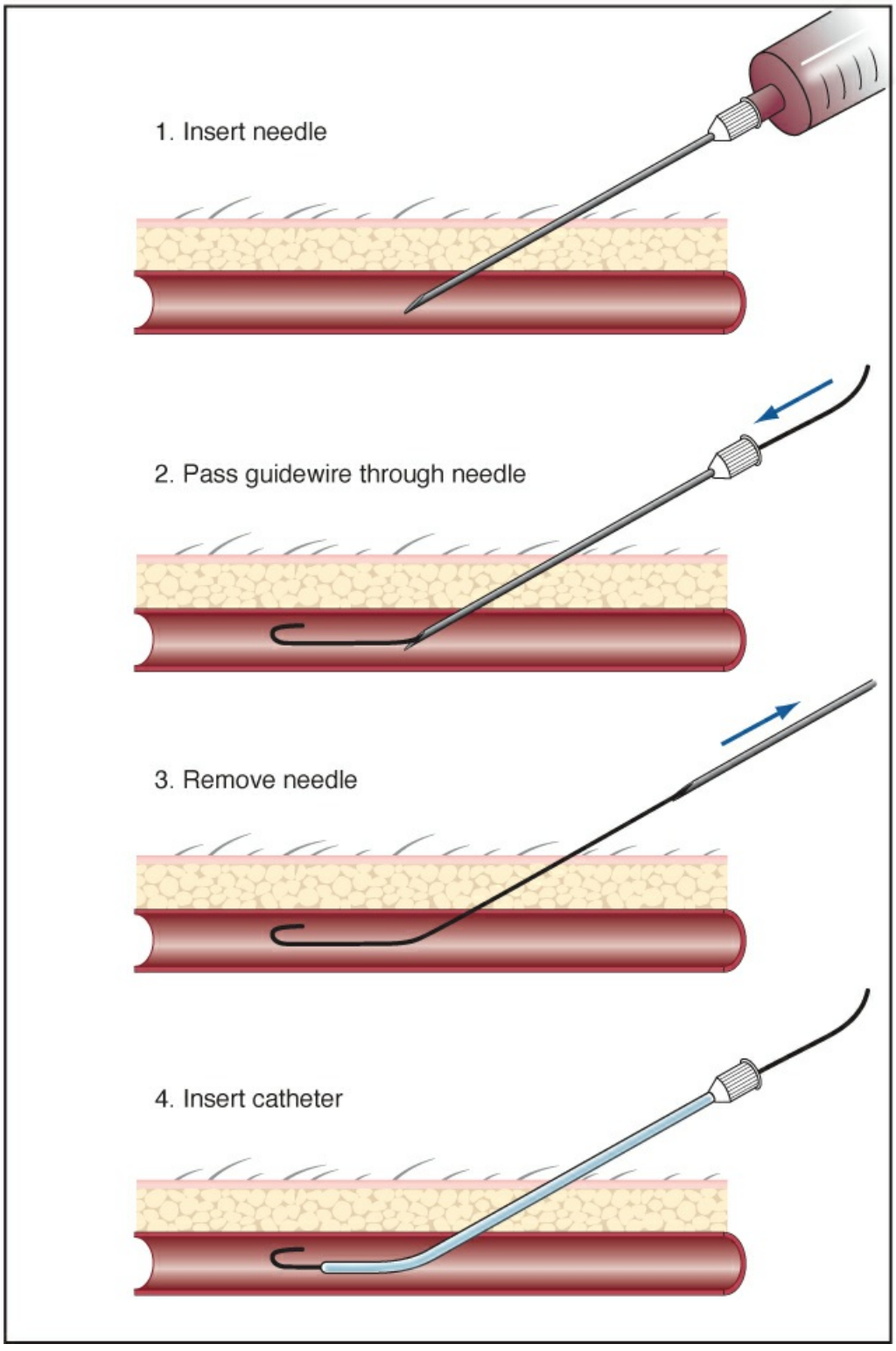

FIGURE 1.5 The steps involved in guidewire-assisted cannulation of blood vessels (the Seldinger technique).

TABLE 1.4 Summary of the General-Purpose Venous Catheters

Type of Catheter	Advantages	Disadvantages
Peripheral Catheters		
Short Catheter	Rapid IV access Low risk of septicemia	Limited dwell time High failure rate
Long Catheter	Longer dwell time than short catheters	Can require ultrasound-guided insertion
Midline Catheter	Longest dwell time of peripheral catheters Multiple lumens Allows prolonged vasopressor infusions	Requires ultrasound-guided insertion and special training
Central Catheters		
Peripherally Inserted Catheter	Less risk, and greater patient acceptance, than central venous catheters	High occlusion rate Increased length can compromise infusion rate
Central Venous Catheter	Most versatile general-purpose catheter	Risk of serious complications

VASCULAR ULTRASOUND

The emergence of real-time ultrasound to guide vascular cannulation has added considerably to the success rate and safety of cannulating both central and peripheral veins (16,17). The following is a brief introduction to the methodology.

The Method

Vascular ultrasound uses linear array probes that emit high-frequency ultrasound waves (5–15 MHz); this produces high-resolution images, but limits the depth of tissue penetration (to about 9 cm). The waves that are reflected back to the probe (called *echoes*) are processed by a transducer that converts the ultrasound waves to gray scale images. Higher amplitude echoes produce brighter or whiter images, while lower amplitude echoes produce darker or blacker images. This methodology is known as B-mode (brightness-mode) ultrasound, and it produces two-dimensional, gray-scale images. Ultrasound waves pass readily through fluids, so blood vessels will have a dark gray or black interior on the ultrasound image.

Orientation of the Beam

The ultrasound beam can be aligned along the long axis of a blood vessel to produce a sagittal image of the vessel (long-axis view), or it can be oriented to transect a blood vessel, which produces a cross-sectional view of the vessel (short-axis view). This is demonstrated in Figure 1.6. Note that in the long-axis view, the probe needle advances along the plane of the ultrasound beam, and can be visualized along its entire path, while in the short-axis view, the probe needle does not meet the ultrasound beam until it reaches the target vessel, where it is visible only as a high-intensity dot on the ultrasound image.

Which View is Better?

Neither view is clearly superior to the other, and each has advantages and disadvantages. The advantage of the short axis view is greater ease in locating the target vein, and the ability to visualize both the vein and its affiliated artery (which reduces the risk of arterial puncture), while the disadvantage is the limited ability to view the probe needle. The long axis view allows visualization of the probe needle, guidewire, and catheter during the cannulation, but is unable to visualize an affiliated artery, and requires a vein that runs a relatively straight course.

At the present time, the short-axis view seems to be the preferred one for locating the target vessel and confirming puncture of the vessel with the probe needle. The long-axis view is preferred for confirming intraluminal placement of the guidewire and catheter (see next).

Protocol

The recommended protocol for ultrasound-guided vascular cannulation includes the following sequential steps (16): a) identify the target vein, b) verify puncture of the vein by the probe needle, and c) confirm intraluminal placement of the guidewire and catheter.

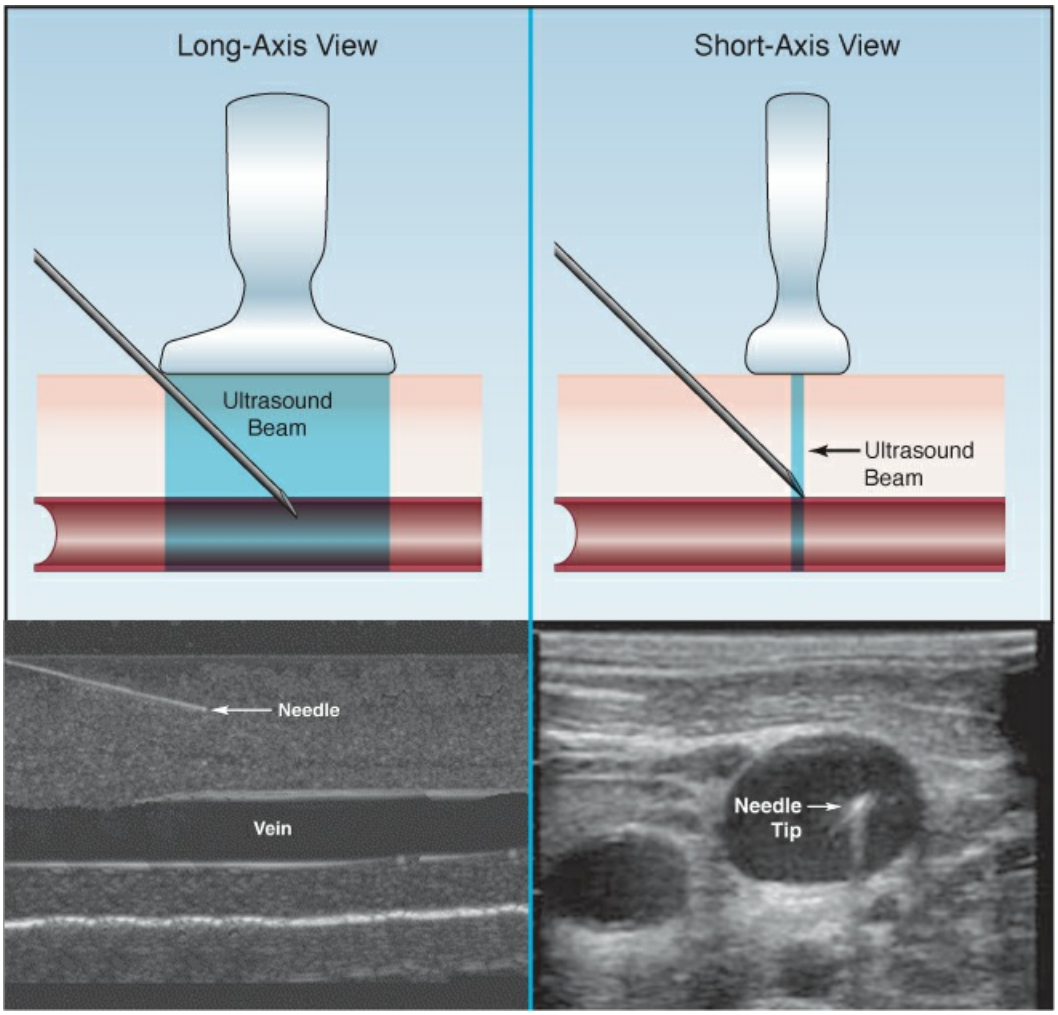

FIGURE 1.6 Orientation of the ultrasound beam in the long-axis and short-axis view, and how this influences the ability to visualize the probe needle. See text for further explanation.

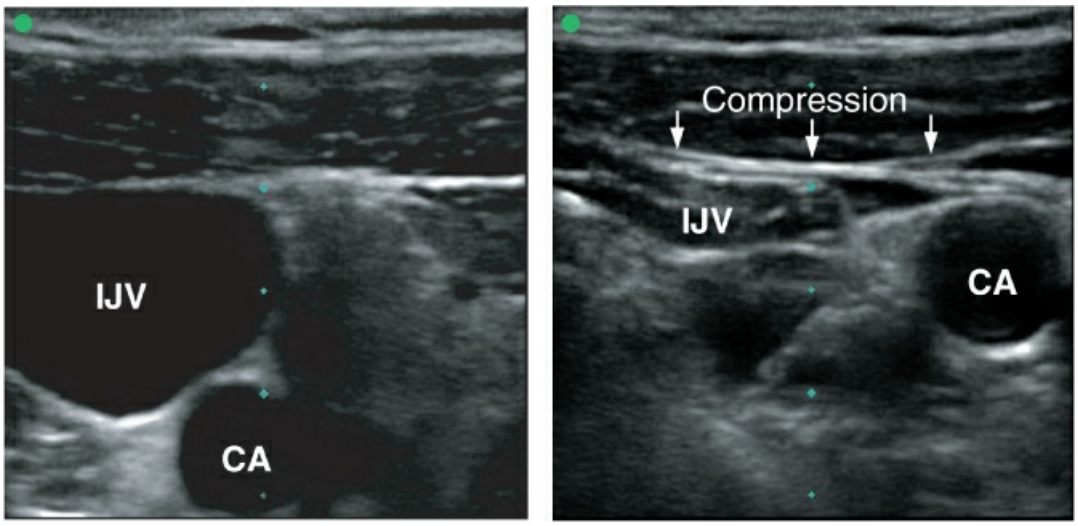

FIGURE 1.7 Compressibility for identifying veins. The image on the left is a short-axis view of the internal jugular vein (IJV) and carotid artery (CA) at the base of the neck, and the image on the right shows compression of the vein when downward pressure is applied to the overlying skin. The green dots mark the lateral side of each image.

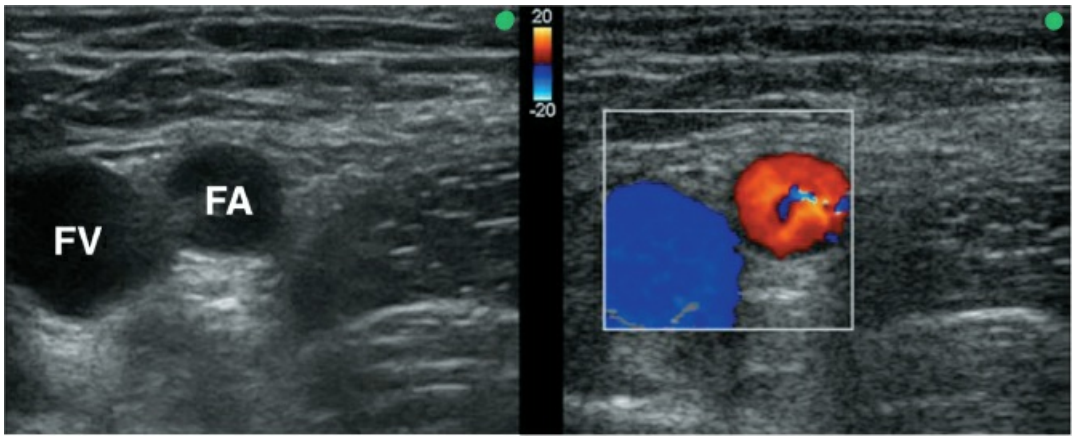

FIGURE 1.8 Color flow Doppler imaging for identifying arteries and veins. The image on the left is a short-axis view of the femoral artery (FA) and femoral vein (FV) in the groin, and the image on the right is a color Doppler image of the same blood vessels showing the artery in red and the vein in blue. The green dots mark the lateral side of each image.

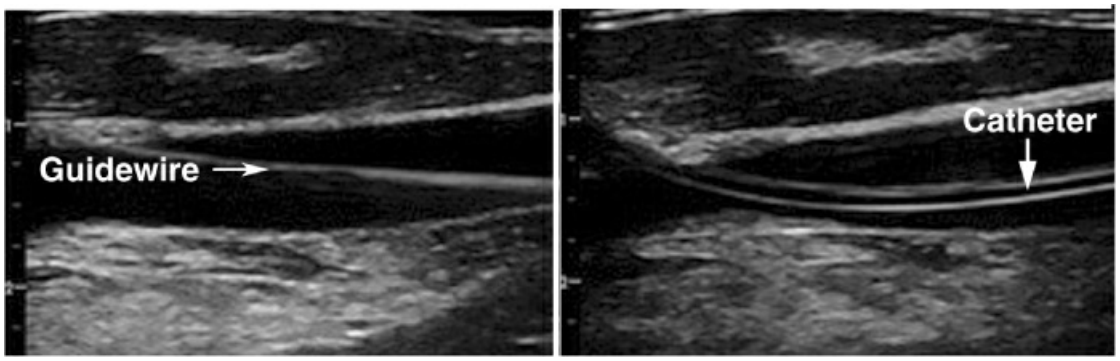

FIGURE 1.9 Long-axis view of the internal jugular vein showing intraluminal placement of the guidewire and catheter. Images from Reference 16.

Distinguishing Veins from Arteries

There are two methods for distinguishing arteries from veins using ultrasonography. The easiest (and most popular) method is to determine the compressibility of the blood vessel; i.e., when pressure is applied to the skin overlying a blood vessel, a vein will collapse much more readily than an artery. This is demonstrated in Figure 1.7, which shows an internal jugular vein that is compressed by pressing down on the overlying skin, while the nearby carotid artery is unaffected. (*Note:* One exception to this behavior is the presence of venous thrombosis, because a vein that is filled with a thrombus will not be compressible).

The other method for identifying arteries and veins is color Doppler imaging, where the frequency shift produced by the direction of blood flow (the Doppler effect) is converted into color images, and superimposed on the gray-scale ultrasound image (18). An example of this is shown in Figure 1.8, with the red color marking the femoral artery and the blue color marking the femoral vein. These colors are not specific for arteries and veins, but instead represent the direction of blood flow in relation to the ultrasound probe. (The color assignments are indicated on the color legend in Fig. 1.8.)

The Probe Needle

Advancing the probe needle to puncture the target vein is easily visualized in the long-axis view, as shown in Figure 1.6. In the short-axis view, the probe needle is advanced using short, stabbing thrusts to produce tissue displacement, which marks the path of the needle, and puncture of the target vein is verified by observing a high-intensity dot in the lumen of the vessel, as shown in Figure 1.6.

Confirming Catheter Placement

Veins tend to collapse when punctured, creating a tendency for probe needles to puncture the posterior wall of the vein. In one study, posterior wall perforation occurred in 40% of ultrasound-guided cannulations using the short-axis view, and 18% of cannulations using the long-axis view (19). Because of this risk (and the popularity of the short-axis view), it is important to confirm that the catheter has been placed in the lumen of the blood vessel. This begins by confirmating that the guidewire has been advanced into the vessel lumen, as shown on the left in Figure 1.9 (16). The catheter can then be advanced over the guidewire, and the intraluminal placement of the catheter is then confirmed, as shown on the right in Figure 1.9.

INTRAOSSEOUS VASCULAR ACCESS

The discovery that fluids could be infused into the marrow cavity of bones and reach the systemic circulation occurred in the mid-1930s. However, this observation gained little attention until the London bombings during World War II, when the poor lighting from the frequent citywide blackouts created difficulties in establishing venous access, and an enterprising surgeon named Hamilton Bailey began infusing fluids into the marrow cavity of the sternum to resuscitate bombing victims (20). Despite early enthusiasm, the intraosseous (IO) route was relegated to obscurity when plastic catheters were introduced for intravenous cannulation (in the 1950s). A rebirth of the IO route occurred in the 1980s, when it was adopted for pediatric resuscitation, and it has subsequently gained favor in adults as an alternative route for emergency

vascular access.

Indications

The principal indication for IO access is the need for emergent vascular access when intravenous (IV) access is problematic, or is not immediately available. This scenario is most likely to occur in patients with cardiac arrest, major trauma, or circulatory shock; in each of these conditions, IO access has proven to be a viable alternative to IV access (21−23). One appealing feature of the IO route is the rigid structure of the medullary cavity and its drainage system, which (unlike veins) will not collapse in the setting of hypotension, hypovolemia, or cardiovascular collapse.

Acceptance of the IO route is demonstrated in the most recent guidelines on advanced life support from the American Heart Association, which recommends proceeding to IO access when an initial attempt at IV access is unsuccessful, or IV access is not feasible (21). Since about two-thirds of cases of cardiac arrest occur outside the hospital (24), the need for IO access occurs primarily in the field. As a result, prehospital personnel (emergency medical technicians and paramedics) have been the major focus of training for IO access, and the success rate in the field is as high as 97% (25). IO access in the field is also important for the early management of major trauma (22), including combat casualties (25), and IO access is included in the knowledge base for Advanced Trauma Life Support (ATLS) certification from the American College of Surgeons (26).

Contraindications

Contraindications to IO access include a fractured or previously entered bone (because of possible leakage of infused fluids), vascular injury in the target extremity, and burn injury, cellulitis, or osteomyelitis at the cannulation site. Osteopetrosis (abnormally dense bone) is also a contraindication (23), but is a rare condition.

Establishing IO Access

There are two popular sites for IO access in adults: the proximal tibia (just below the knee), and the proximal humerus (just below the shoulder). The proximal tibia has two advantages: a higher success rate (25,27), and a location that does not interfere with intubation or chest compressions. The proximal humerus has the advantage of a higher flow capacity (28), but the proximal tibia is the favored site in adults.

The Proximal Tibia Site

The access site in the proximal tibia is on a flat surface of bone just below the medial condyle (see Figure 1.10). The point of needle insertion is 3 cm below the inferior tip of the patella, and 2 cm medial to that point.

Inserting the Needle

Inserting the IO needle can be done manually, but a powered “needle driver” is preferred. A popular choice in recent years is a battery-powered device like the one shown in Figure 1.10 (28,29). There are three different IO needles that attach to this device: each is a 15 gauge needle, available in lengths of 15 mm (for children), 25 mm (for average-sized adults), and 45 mm (for large or obese adults). The appropriate length for an individual patient can be determined by first

advancing a probe needle until it hits the bone. (In awake patients, the probe needle should also be used to inject lidocaine locally, especially at the level of the periosteum, which is well endowed with pain fibers.) The IO needles have horizontal markers, and the measured distance from the skin to the periosteum should leave the horizontal marker closest to the hub of the needle at or slightly above the skin surface.

After appropriate skin antisepsis (sterile gloves are not required for inserting IO needles), the IO needle is advanced manually until it hits the bony surface of the tibia. The needle driver is then attached and, with the needle at an angle of 90° from the skin surface, the needle driver is engaged. This will spin the needle in a clockwise direction, and the needle is then advanced while applying downward pressure, until a sudden loss of resistance indicates entry into the medullary cavity. This should be verified by the aspiration of blood. This is not always possible, because bone marrow is viscous (like a jelly), which can prevent the aspiration of blood. Flushing the needle with 5–10 mL of saline can liquify enough marrow to correct this problem.

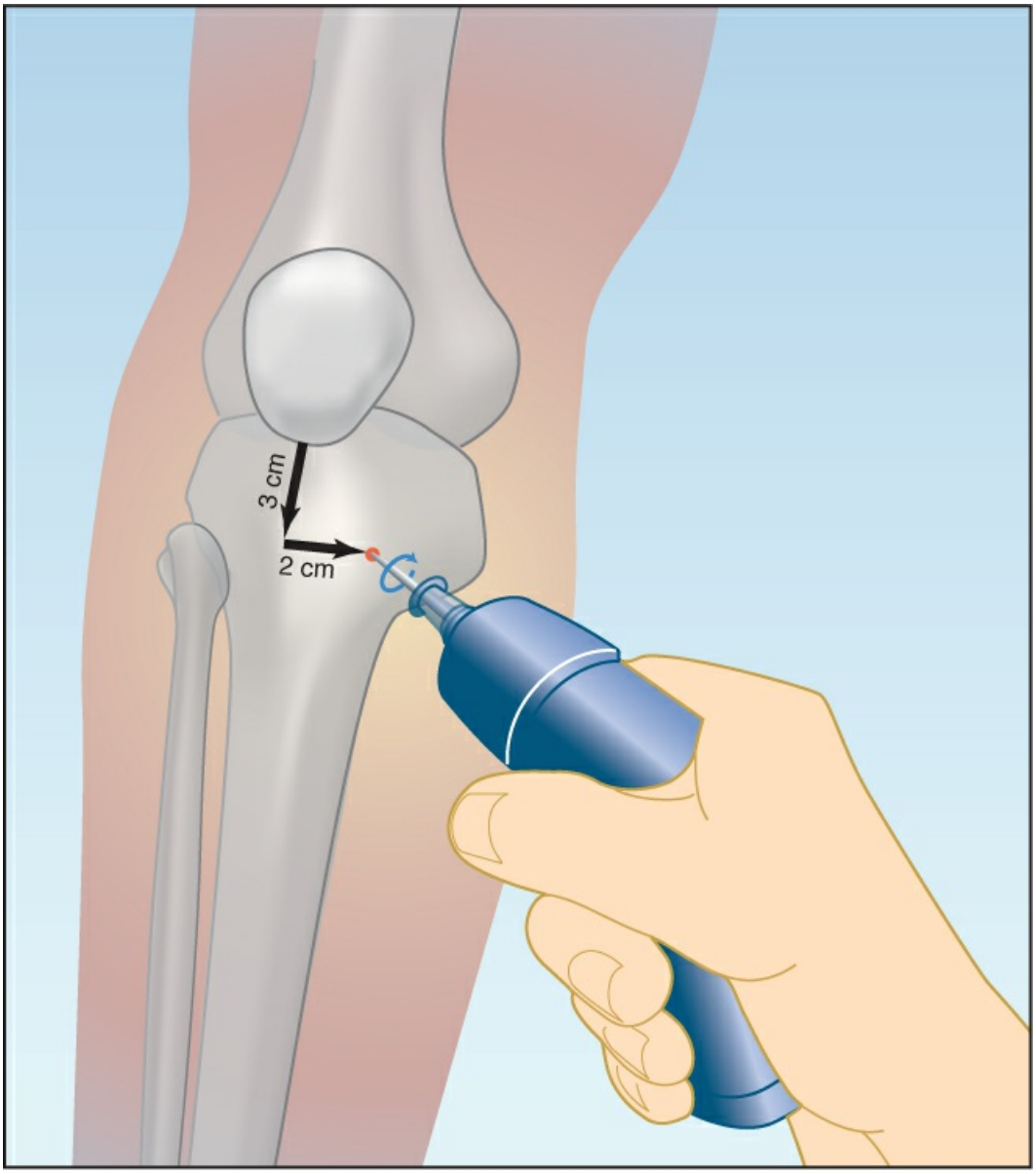

FIGURE 1.10 Illustration depicting the insertion of an intraosseous needle into the proximal femur, of the right leg and the surface measurements used to identify the insertion point. A battery powered needle driver is used to advance the needle into the marrow cavity. See text for further explanation.

Pre-Infusion Pain Control

The infusion of fluids into the marrow cavity is painful, presumably from stretching the periosteum. Therefore in awake patients, lidocaine injection into the medullary cavity is advised prior to infusing fluids. The recommended protocol is as follows (23,30):

. Use a 2% solution (20 mg/mL) of preservative-free lidocaine for intravenous use, and inject 40 mg (2 mL) into the marrow cavity over 2 minutes.

. Allow lidocaine to dwell for one minute, then flush with 10 mL of saline.

. Start the desired IO infusion. If pain relief is incomplete, readminister lidocaine at half the

initial dose (20 mg) over one minute.

The lidocaine effect may be lost after one hour, and additional analgesia may be necessary. Intraosseous fentanyl (in the usual IV doses) can be used for this purpose.

IO Infusions

Intraosseous infusions are relatively sluggish, with flow rates that are about 25% of peripheral vein infusions (22,23). This is due to the viscous nature of bone marrow, and the relatively high pressure in the marrow cavity (which averages about 30 mm Hg). To counter the sluggish flow rates, IO infusions are routinely pressurized (with infusion pumps or inflatable pressure bags). However, pressures of 300 mm Hg or even higher may be inadequate for replacing massive blood loss, and dual IO infusions have been advocated by some in this situation (22).

Intraosseous access is considered a temporary intervention, and IO infusions are not recommended for longer than 24 hours (26). (There is, however, no firm evidence to validate this recommendation.) When IO infusions are discontinued, the IO needle is removed by attaching a luer-lock syringe and slowly rotating the needle in a clockwise direction as it is pulled upward at a 90° angle with the skin surface. (Rocking the needle back and forth to facilitate removal is not advised, and will promote leakage from the bone.)

Complications

Complications of IO access are infrequent (possibly due to its limited lifespan), with several studies showing complication rates below 1% (22,23). Potential complications include skin abscesses, osteomyelitis, tibial fracture, compartment syndrome, and fat or marrow emboli (22,23,30,31).

A FINAL WORD

One of the rarest sights in any ICU is a patient with no intravenous access. While this may not be a revelation, it does indicate that a working knowledge of vascular access has universal relevance for patient care in the ICU. This chapter is a first step in acquiring that knowledge. The following points in the chapter deserve emphasis.

. Infusion rates are influenced by the dimension of a vascular catheter, not by the size of the cannulated vein.

. The radius (lumen size) of a catheter has a much greater influence on flow than the length of the catheter. For rapid infusions, a large bore catheter is desirable, and a short, large-bore catheter is optimal.

. Midline catheters (15 – 20 cm catheters inserted into one of the major veins above the antecubital fossa) have become a popular choice for extended venous access, and can be used for prolonged vasopressor infusions.

. Real-time ultrasonography has become an essential tool for cannulating veins that are not visible or palpable.

. The intraosseous (IO) route is recommended for emergency vascular access when intravenous access is problematic, or not immediately available. The proximal femur is a popular site for IO access because the procedure does not interfere with intubation or chest compressions.

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Chapter 2

Central Venous Access

Good doctors leave good tracks.

J. Willis Hurst, MD (*a*)

As a medical student in the early 1970s, I recall that vascular access was achieved almost exclusively by inserting narrow-bore needles into superficial veins in the arms (or wherever we could find them). The practice of inserting flexible plastic catheters into larger, more centrally placed veins was in its infancy (e.g., cannulation of the internal jugular vein was introduced only a few years earlier, in 1969) (1), and the procedure was often performed in the operating room, using a skin incision to introduce the (single-lumen) catheters, and forceps to advance the catheters through the subcutaneous tissues.

Now fast forward to modern times, and central venous access is a staple of patient care in ICUs, with multilumen catheters inserted percutaneously at the bedside, using real-time ultrasonography to guide the cannulation process (as described in Chapter 1). Central venous cannulation has become an essential skill for the care of critically ill patients, and this chapter will supplement the procedural skill (which must be acquired at the bedside) by presenting the relevant considerations involved in establishing central venous access.

CONSIDERATIONS IN PREVENTION

Central venous catheters have risks that far outweigh those of peripheral vein catheters (2), so the decision to insert a central venous catheter has implications for patient safety. There are, however, safer alternatives to central venous catheters in certain situations, as described next.

Shrinking Indications

The following are the traditional indications for inserting a central venous catheter.

. When peripheral venous access is difficult to obtain or maintain.

. For prolonged venous access (i.e., more than a few days).

. When multiple intravenous therapies are required (taking advantage of the multilumen

capabilities of central venous catheters).

. For the infusion of vasopressors, hypertonic fluids (including total parenteral nutrition), or vesicants (e.g., antineoplastic agents).

. For patients with life-threatening hemodynamic instability.

. For specialized interventions, such as acute hemodialysis, temporary transvenous pacing, or invasive hemodynamic monitoring.

It is now possible to avoid central venous access for many of the traditional indications, thanks to the emergence of midline catheters and peripherally inserted central catheters (PICCs). These catheters are described in Chapter 1. Both are inserted in the arm, just above the antecubital fossa (see Figure 1.3), and both can be used for prolonged venous access (especially PICCs, which can remain in place for months), and for infusions of vasopressors and hypertonic fluids (3). These catheters are also available with multiple lumens, for patients who require multiple intravenous therapies. Central venous access is still preferred for patients with life-threatening hemodynamic instability (circulatory shock), and it is mandatory for specialized interventions like acute hemodialysis. Thus, 4 of the 6 traditional indications for central venous access have alternative solutions.

Midline catheters and PICCs have fewer risks than central venous catheters (e.g., there is no risk of pneumothorax because the catheters are inserted in the arm) and they are more readily accepted by patients. Because of these advantages, the demand for central venous catheters is steadily declining (4), and midline catheters are becoming the preferred replacement (5).

Contraindications

There are no absolute contraindications to central venous cannulation, including the presence or severity of a coagulation disorder (6,7). There is a recommendation to correct a platelet count that is <20,000 x 10^6/L or an INR >3 prior to catheter insertion (7), but there is no evidence to support this recommendation.

Infection Control Measures

Infection control is an essential part of vascular cannulation, and the preventive measures recommended for central venous access are shown in Table 2.1 (8). When used together as a “bundle”, these measures have been effective in reducing the incidence of catheter-related bloodstream infections (9–11). The following is a brief description of these preventive measures.

TABLE 2.1 The Central Line Insertion Bundle

Components	Recommendations
Hand Hygiene	Use an alcohol-based, waterless hand rub or a soap and water handwash before and after: a) palpating the catheter insertion site, or b) inserting, replacing, or manipulating the catheter..
Barrier Precautions	Use maximal barrier precautions, including cap, mask, sterile gloves, sterile gown, and sterile full body drape, for catheter insertion or guidewire exchange.
Skin Antisepsis	Scrub the insertion site with 2% chlorhexidine -70% alcohol solution for 30 seconds, and allow to dry completely..

Cannulation Site	When possible, avoid femoral vein cannulation.

From References 8–12.

Hand Hygiene

Proper hand hygiene is considered one of the most important, and most neglected, methods of infection control. Alcohol-based, waterless hand rubs are preferred, if available; otherwise, handwashing with soap (plain or antimicrobial soap) and water is acceptable (8,12). Hand hygiene should be performed before and after palpating catheter insertion sites, and before and after donning gloves to insert, replace, or manipulate catheters.

Skin Antisepsis

The catheter insertion site should be decontaminated just prior to cannulation, and the preferred antiseptic agent is chlorhexidine (usually in alcohol). This preference is based on clinical studies showing that chlorhexidine is superior to other antiseptic agents for limiting the risk of catheter-associated infections (13). The enhanced efficacy of chlorhexidine is attributed to its prolonged (≥6 hours) antimicrobial activity on the skin, which is maximized if allowed to air-dry on the skin (14). The drying time is typically 30 seconds for dry skin, and up to 2 minutes for moist skin (11).

Barriers

All vascular cannulation procedures, except those involving small peripheral veins, should be performed using full barrier precautions, which includes caps, masks, sterile gloves, sterile gowns, and a sterile drape from head to foot. (*Note*: The only barrier precaution advised for peripheral vein cannulation is the use of gloves, and nonsterile gloves are acceptable as long as the gloved hands do not touch the catheter) (8).

Site Selection

Cannulation of the femoral vein is considered the least desirable of the central venous access sites, primarily due to an increased risk of thrombosis with femoral vein catheters (15). When the central line bundle was introduced, there was also a higher risk of catheter-related septicemia with femoral catheters. However, *studies in more recent years have shown no increase in the risk of catheter-related septicemia with femoral catheters* (16). This is attributed to increased attention to infection control measures, and the current belief is that *the risk of catheter-related bloodstream infections is not related to the location of the insertion site, but rather to how the site is maintained* (in terms of infection control measures) (11).

INTERNAL JUGULAR VEIN

The most popular site for central venous access is the internal jugular vein at the base of the neck. The right side is preferred because the vessels run a relatively straight course, which reduces the risk of catheter misplacement.

Anatomy

The internal jugular vein (IJV) is located under the sternocleidomastoid muscle on either side of the neck, and it runs obliquely down the neck along a line drawn from the pinna of the ear to the sternoclavicular joint. In the lower neck region, the vein is typically located just anterior and lateral to the carotid artery (although anatomic relationships can vary), and both vessels run through the triangle created by the two heads of the sternocleidomastoid muscle (see Figure 2.1). At the base of the neck, the IJV and subclavian vein join to form the innominate vein, and the convergence of the right and left innominate veins forms the superior vena cava.

Cannulation Techniques

Positioning

Tilting the body so the head is below the horizontal plane (the Trendelenburg position) distends the IJV to facilitate cannulation, and increases venous pressure to reduce the risk of air embolism. In healthy subjects, a head-down body tilt to 15° is associated with a 20–25% increase in the diameter of the IJV, while greater degrees of tilt have no further effect (17). Thus, *only a limited (15°) body tilt is needed for IJV cannulation*. The head-down tilt is not necessary (and is usually not tolerated) in patients with venous congestion (e.g., from heart failure), and it is not advised in patients with increased intracranial pressure.

The head should be rotated slightly in the opposite direction to straighten the course of the vein. Excessive head rotation (beyond 40° from midline) pulls the IJV over the carotid artery, and this overlap increases the risk of carotid artery puncture (18). This risk is highlighted by evidence of posterior wall puncture in as many as 40% of ultrasound guided IJV cannulations (19).

Ultrasound Guidance

When real-time ultrasound is used to guide cannulation of the IJV, there is an increased success rate, fewer cannulation attempts, a shorter time to cannulation, and a reduced risk of carotid artery puncture (20). As a result, ultrasound guidance is a standard practice for catheterization of the IJV (21). (*Note:* The technique of ultrasound-guided vascular cannulation is described in Chapter 1.)

The IJV is well suited for ultrasound imaging because it is close to the skin, and there are no intervening structures to interfere with transmission of the ultrasound beam. A short-axis (cross-sectional) view of the IJV on the right side of the neck is shown in Figure 2.2. This image was obtained by placing the ultrasound probe at the apex of the triangle formed by the clavicular and sternal heads of the sternocleidomastoid muscle. (The probe should be oriented so it transects the muscle.) Note that the IJV is anterior and lateral to the carotid artery, and that there is some overlap of the vessels. This overlap creates the risk of carotid artery puncture, as explained earlier, and mandates that intraluminal placement of the catheter is confirmed. (See Figure 1.9.)

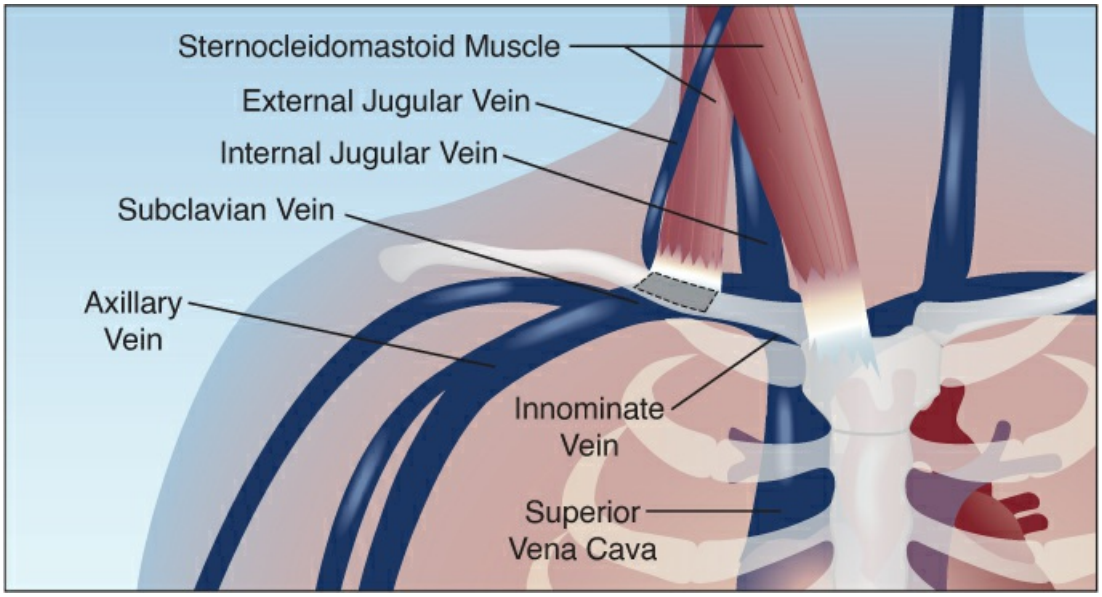

FIGURE 2.1 Anatomic relationships of the veins entering the thorax at the base of the neck.

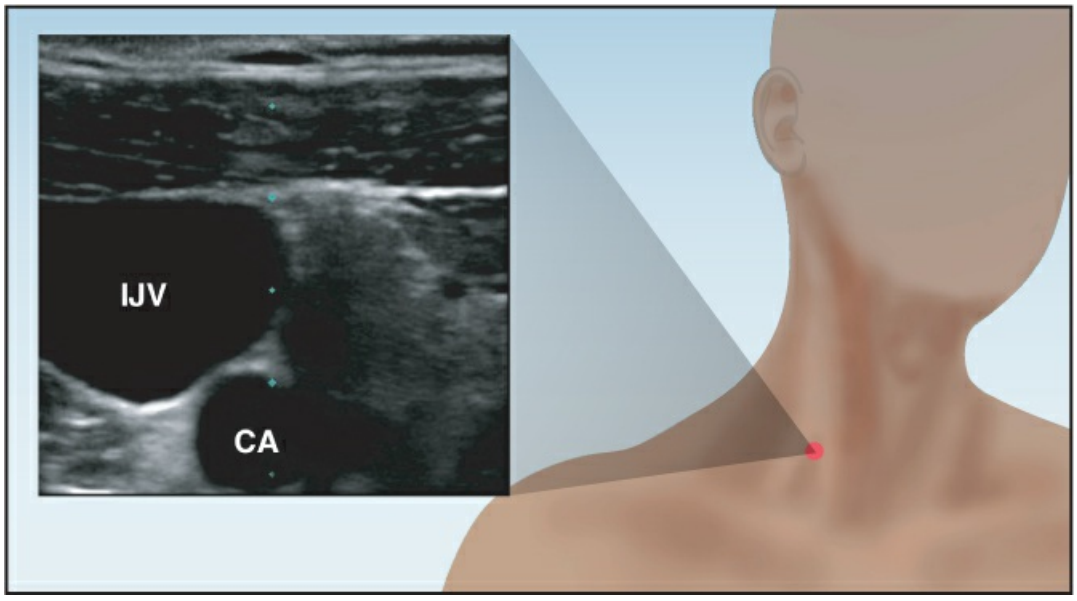

FIGURE 2.2 Short-axis view of the internal jugular vein (IJV) and carotid artery (CA), obtained by placing the ultrasound probe at the apex of the triangle formed by the two heads of the sternocleidomastoid muscle. The green dot marks the lateral side of the image. See text for further explanation.

Landmark Method

When ultrasound imaging is not available, cannulation of the IJV is guided by surface landmarks. There are two approaches using surface landmarks, as described next.

ANTERIOR APPROACH: For the anterior approach, the operator first identifies the triangular area at the base of the neck created by the separation of the two heads of the sternocleidomastoid muscle (see Figure 2.1). The IJV and carotid artery run through this triangle. The operator first locates the carotid artery pulse in this triangle; once the artery is located by palpation, it is gently

retracted toward the midline and away from the IJV. The probe needle is then inserted at the apex of the triangle (with bevel facing up) and the needle is advanced toward the ipsilateral nipple at a 45° angle from the skin. If the vein is not entered by a depth of 5 cm, the needle should be drawn back and advanced again in a more lateral direction.

POSTERIOR APPROACH: For the posterior approach, the insertion point for the probe needle is 1 cm above the point where the external jugular vein crosses over the lateral edge of the sternocleidomastoid muscle. The probe needle is inserted at this point (with the bevel at 3 o'clock) and then advanced along the underbelly of the muscle in a direction pointing to the suprasternal notch. The internal jugular vein should be encountered 5 to 6 cm from the insertion point.

Complications

Accidental puncture of the carotid artery is the most feared complication of IJV cannulation. In a review of six randomized controlled trials of IJV cannulation by experienced operators, the summed incidence of carotid artery puncture was 9.2% when anatomic landmarks were used, and 1.8% with ultrasound guidance (20). If the carotid artery is punctured by the small-bore probe needle, it is usually safe to remove the needle and compress the site for at least 5 minutes (double the compression time for patients with a coagulopathy). Insertion of a catheter into the carotid artery is more of a problem because removing the catheter can be fatal (22,23). *If confronted with accidental cannulation of the carotid artery, leave the catheter in place and consult a vascular surgeon or interventional radiologist.*

TABLE 2.2 Site-Specific Risks of Infection and Thrombosis

	IJV	SV	FV
Number of Catheters	845	843	844
Bloodstream Infection	0.5%	1.4%	1.2%
Symptomatic DVT	0.5%	0.9%	1.4%

Data from Reference 15. IJV = internal jugular vein, SV = subclavian vein, FV = femoral vein.

Other mechanical complications (e.g., hemo/pneumothorax) are less common, and have an aggregated incidence of 2% when anatomic landmarks are used, and <1% with ultrasound guidance (20). Finally, the risk of catheter-related septicemia with IJV catheters is slightly higher than the risk with subclavian catheters (15), but the difference is small (0.5% vs 1.4%, see Table 2.2), and the infectious risk at both sites is considered equivalent (11).

SUBCLAVIAN VEIN

The subclavian vein was once the favored site for central venous access, but the emergence of ultrasound guidance has eroded its popularity because of interference from the overlying clavicle.

Anatomy

The subclavian vein is a continuation of the axillary vein as it passes over the first rib (see Figure 2.1). It runs most of its course along the underside of the clavicle (sandwiched between the clavicle and the first rib), and at some points is only 5 mm above the apical pleura of the lungs. The underside of the vein sits on the anterior scalene muscle along with the phrenic nerve, which comes in contact with the vein along its posteroinferior side. Situated just deep to the vein, on the underside of the anterior scalene muscle, is the subclavian artery and brachial plexus. At the thoracic inlet, the subclavian vein meets the internal jugular vein to form the innominate vein. The subclavian vein is 3–4 cm in length, and the diameter is 7–12 mm in the supine position (24). The diameter of the vein does not vary with respiration (unlike the IJV), which is attributed to strong fascial attachments that fix the vein to surrounding structures and hold it open (24). These attachments may also prevent collapse of the vein with volume depletion.

Cannulation Techniques

Positioning

The head-down body tilt (Trendelenburg position) to 15° increases the diameter of the subclavian vein by about 10%, with no further effect from greater degrees of tilt (14). Despite this minimal effect, the increase in venous pressure in the Trendelenburg position (which reduces risk of air embolism) has justified the recommendation for the head-down body tilt during subclavian vein cannulation (25). Other popular maneuvers (aimed at bringing the subclavian vein closer to the clavicle), such as turning the head or placing a rolled towel under the shoulder, are not advised because they decrease the cross-sectional area of the vein (24,26).

Ultrasound Guidance

The use of real time ultrasound improves the success rate of subclavian vein cannulation (from 82% to 97%) and decreases the complication rate (from 30% to 11%) (27). However as mentioned earlier, ultrasound imaging is a challenge for the subclavian vein because of interference from the overlying clavicle. The vein can be visualized from above or below the clavicle, but the infraclavicular approach is the popular choice.

INFRACLAVICULAR APPROACH: This approach begins by identifying the clavicular head of the sternocleidomastoid muscle and its insertion on the clavicle; this marks the portion of the clavicle that overlies the subclavian vein (as shown in Figure 2.1). Orient the ultrasound probe so it transects the clavicle (with the orientation marker pointing cephalad), and place the probe just below the lower edge of the clavicle in this region. This should produce a short-axis view like the image in Figure 2.3, which includes the subclavian vein and artery, as well as the apical pleura. Note the proximity of the subclavian vein to the apical pleura, highlighting the risk of pneumothorax during the cannulation procedure.

Identifying the subclavian vein by compression may not be possible because of the overlying clavicle, and color Doppler imaging may be necessary (see Figure 1.8). At the end of the cannulation procedure, the pleural line should be inspected for evidence of *lung sliding* to rule out iatrogenic pneumothorax (see later).

Landmark Method

To cannulate the subclavian vein without ultrasound, first mark the region of the clavicle that overlies the subclavian vein, as shown in Figure 2.1. The vein can be entered from above or below the clavicle in this region, but the infraclavicular approach is the popular route.

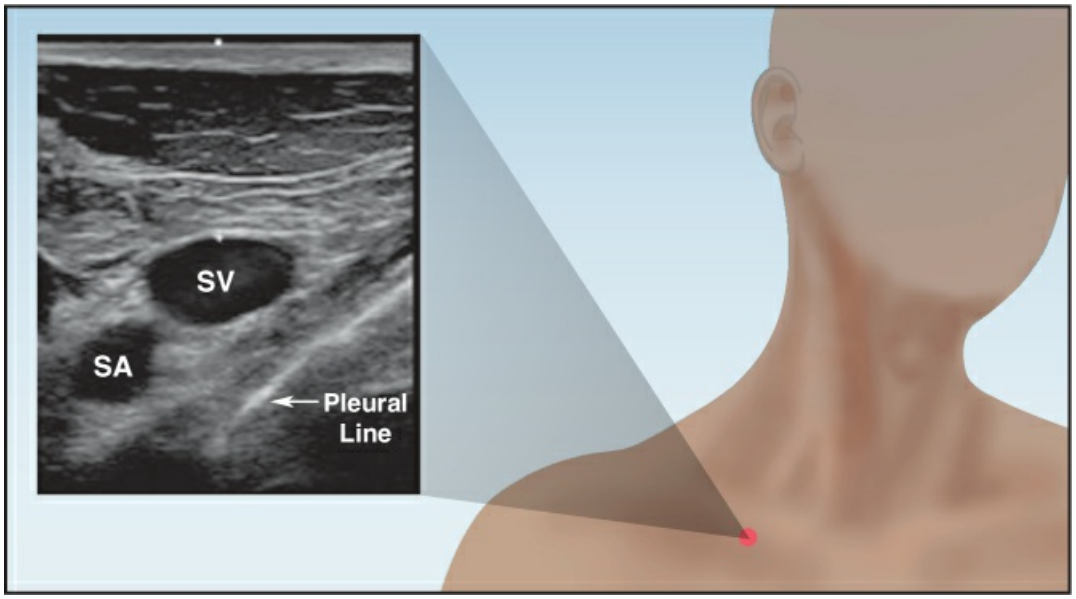

FIGURE 2.3 Infraclavicular, short-axis view of the subclavian vein (SV), subclavian artery (SA), and apical pleura, obtained by placing the ultrasound probe just below the clavicle in the region where it overlies the subclavian vein. See text for further explanation. Ultrasound image from Reference 25.

INFRACLAVICULAR APPROACH: At the lateral edge of the marked area, insert the probe needle (with the bevel at 12 o'clock) just below the clavicle, and advance the needle along the underside of the clavicle, in the direction of the suprasternal notch. The needle should enter the subclavian vein within a few centimeters. When the vein is punctured, turn the bevel to 3 o'clock to help direct the guidewire into the superior vena cava. It is important to keep the needle on the underside of the clavicle to avoid puncturing the subclavian artery (which lies deep to the subclavian vein) and the apical pleura.

In obese patients, the subclavian vein can be more deeply situated, and a deeper trajectory for the probe needle may be needed. This creates the risk for puncture of the subclavian artery or apical pleura. *In morbidly obese patients, the depth of the subclavian vein can exceed the reach of the probe needle* (26). For these reasons, the landmark approach to subclavian vein cannulation should be avoided, if possible, in morbidly obese patients.

Complications

The acute complications of subclavian vein cannulation (using ultrasound to landmark rates) include puncture of the subclavian artery (1% to 6%), pneumothorax (1% to 4%), brachial plexus injury (0% to 3%), phrenic nerve injury (0% to 2%), and catheter malposition (8% to 9%) (27). Complications associated with indwelling catheters include septicemia, thrombosis, and subclavian vein stenosis. The latter complication appears days or months after catheter removal,

and has a reported incidence of 15–50% (28). The risk of stenosis is the principal reason to *avoid cannulation of the subclavian vein in patients who might require long-term hemodialysis access in the ipsilateral arm.*

FEMORAL VEIN

The femoral vein is considered the least desirable site for central venous access, although the unfavorable reputation is mostly undeserved (see later).

Anatomy

The femoral vein is a continuation of the long saphenous vein in the groin, and is the main conduit for venous drainage of the legs. It is located in the femoral triangle along with the femoral artery and nerve, as shown in Figure 2.4. The superior border of the femoral triangle is formed by the inguinal ligament, which runs from the anterior superior iliac spine to the pubic symphysis, just beneath the inguinal crease on the skin. At the level of the inguinal ligament (crease), the femoral vein lies just medial to the femoral artery, and is only a few centimeters from the skin. The vein is easier to locate and cannulate when the leg is placed in abduction.

Cannulation Techniques

Real-time ultrasound is recommended for femoral vein cannulation (21), although there is little evidence of benefit with ultrasound at this site (29).

Positioning

Elevation of the upper body to 15° above horizontal (the ”reverse” Trendelenburg position) can increase the cross-sectional area of the femoral vein by about 50% (30), so mild upper body elevation should be advantageous, especially for the landmark approach. Placing the leg in abduction is also recommended to facilitate the cannulation procedure.

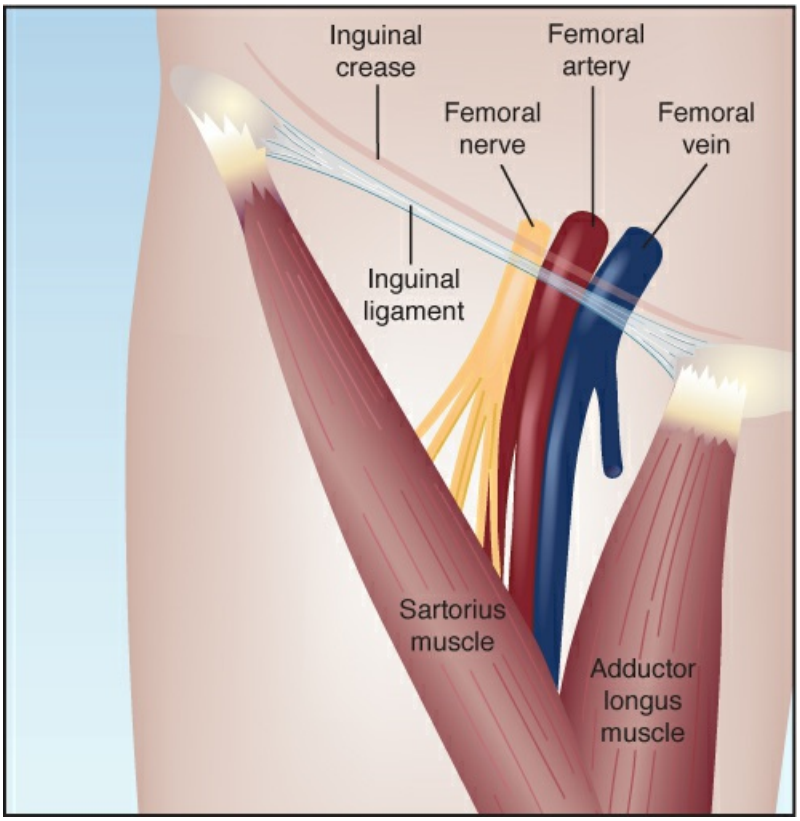

FIGURE 2.4 Anatomy of the femoral triangle.

Ultrasound Guidance

Ultrasound visualization of the femoral artery and vein is possible by placing the ultrasound probe over the femoral artery pulse, which is typically located just below and medial to the midpoint of the inguinal crease. A short-axis view of the femoral artery and femoral vein in this location is shown in Figure 1.8. Note that the vein lies a little deeper than the artery.

Landmark Method

To cannulate the femoral vein without ultrasound imaging, begin by locating the femoral artery pulse just below the inguinal crease. Then insert the probe needle (with the bevel at 12 o'clock) 1–2 cm medial to the pulse, and the vein should be entered at a depth of 2 to 4 cm from the skin. If the femoral artery pulse is not palpable, draw an imaginary line from the anterior superior iliac crest to the pubic tubercle, and divide the line into three equal segments. The femoral artery should be just underneath the junction between the middle and medial segments, and the femoral vein should be 1–2 cm medial to this point. This approach has a reported success rate of >90% (31).

Complications

The principal concerns at the femoral site are thrombosis and septicemia, which are considered enough of a risk to discourage femoral vein cannulation (as indicated in Table 2.1). However, study results like those in Table 2.2 (15) are not as foreboding as advertised. These results (from a multicenter study that included 2,532 central venous catheters) show a remarkably low rate of

infectious and thrombotic complications at all sites. The risk of catheter-related septicemia at the femoral site was actually lower than the risk at the internal jugular vein site (the favored site for central venous access). The femoral site did have the highest risk of symptomatic deep vein thrombosis (DVT), but the overall risk was minor (1.5%). Results like these are supported by other studies (32), and they demonstrate the safety of the femoral vein site for central venous access.

IMMEDIATE CONCERNS

Venous Air Embolism

Air entry into the venous circulation is an uncommon but potentially lethal complication of central venous cannulation (33).

Pathophysiology

Pressure gradients that favor the movement of air into the venous circulation are created by the negative intrathoracic pressure generated during spontaneous breathing. A pressure gradient of only 5 mm Hg across a 14 gauge catheter (internal diameter = 1.8 mm) can entrain air at a rate of 100 mL per second, and this is enough to produce a fatal venous air embolism (34).

The impact of air entry into the venous circulation is determined by the volume of air and the rate of entry. The outcome can be fatal when air entry reaches 200–300 mL (3–5 mL/kg) over a few seconds (34). Entrained air can produce an air lock in the right ventricle, leading to acute right heart failure and cardiogenic shock, while air reaching the pulmonary circulation can produce leaky-capillary pulmonary edema (33,34). Finally, air can pass through a patent foramen ovale and produce an acute embolic stroke.

Prevention

The standard preventive measure for air embolism is the head-down body tilt (the Trendelenburg position) to increase venous pressure during cannulation of the internal jugular and subclavian veins. Elevation of the upper body (the reverse Trendelenburg position) is not necessary as a preventive measure during femoral vein cannulation because femoral vein catheters do not enter the thorax and thus are not exposed to negative pressures.

Clinical Presentation

Venous air entry can be clinically silent (33). In symptomatic cases. the earliest manifestation is sudden onset of dyspnea, which may be accompanied by a distressing cough. This can progress rapidly to acute respiratory failure and circulatory shock. In the most advanced cases, the mixing of air and blood in the right ventricle can produce a splashing auscultatory sound called a ‘mill wheel’ murmur (35).

Venous air embolism is usually a clinical diagnosis. Transesophageal echocardiography is considered the most sensitive method of detecting air in the right heart (capable of detecting as little as 0.02 mL/kg) (33), but this procedure is often not readily available. Precordial Doppler ultrasound can be useful (air in the cardiac chambers produces a high-pitched sound), but the Doppler signal can lack specificity (33).

Management

The following measures are recommended for the management of venous air embolism (33,34), although their efficacy is unproven.

. If air entrainment is suspected through an indwelling catheter, attach a syringe to the catheter and attempt to aspirate air from the bloodstream.

. Place the patient on 100% oxygen (to promote the movement of nitrogen out of the air bubbles in the bloodstream, and thereby decrease the volume of entrained air.

. Place the patient in the left lateral decubitus position (to move an air pocket that is blocking the outflow of the right ventricle).

. For patients with cardiovascular collapse, consider extracorporeal support.

Pneumothorax

Pneumothorax is a feared but infrequent complication of central venous access, and most cases are associated with subclavian vein cannulation (where the incidence is 1% using ultrasound and 4% otherwise) (27). The detection of post-procedure pneumothoraces can be problematic, as explained next.

Portable Chest Radiography

The portable chest x-ray has been the standard method for detecting pneumothorax after central venous cannulation, but clinical studies have shown that *portable chest x-rays fail to detect as many as 50% of pneumothoraces in critically ill patients* (36,37). This lack of sensitivity is attributed to the supine position (which is the position of most patients in the ICU during portable chest radiography), because pleural air does not collect at the apex of the lungs in the supine position, but instead collects in the anterior region of the pleural cavity (which can be close to the base of the lung) (38,39). Pleural air in this location will be in front of the lungs, and can be missed on a portable chest x-ray because of the lung markings behind the pleural air. An example of an anterior pneumothorax that is not apparent on a supine chest x-ray is shown in Figure 2.5.

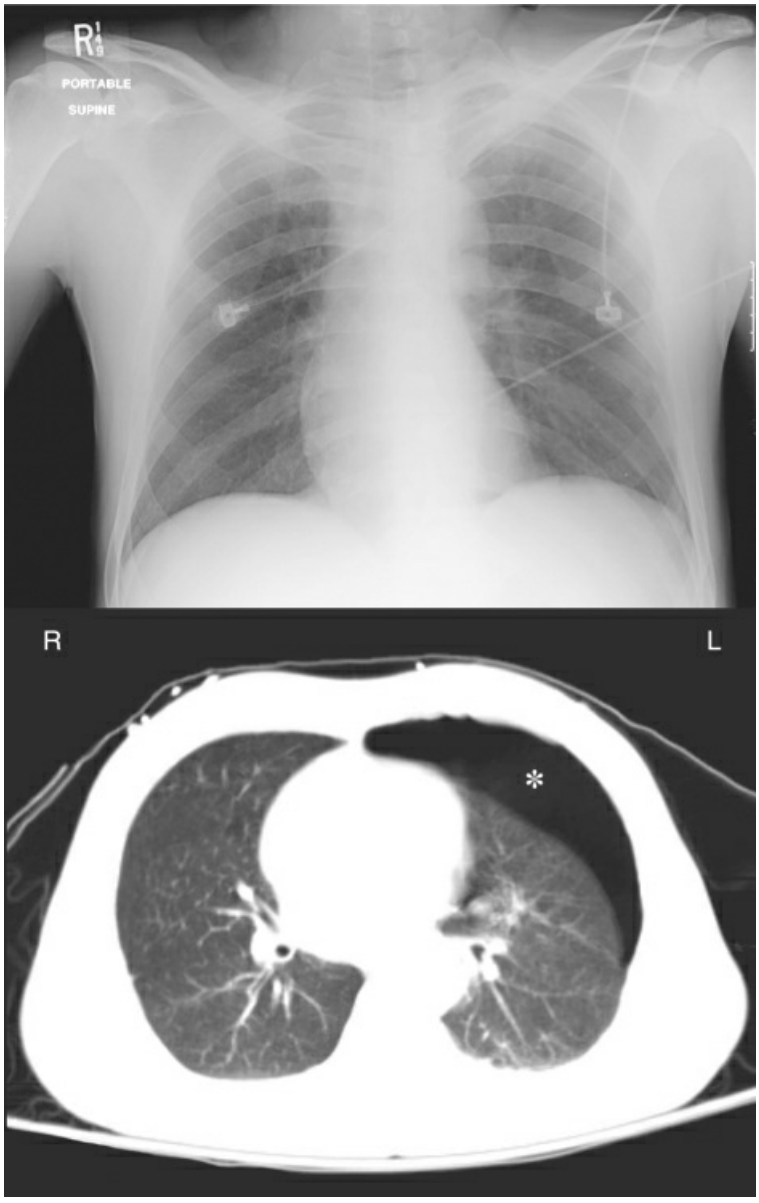

FIGURE 2.5 Portable chest x-ray and CT image of the chest in a young male with blunt chest trauma. The chest film is unrevealing, while the CT image shows an anterior pneumothorax (indicated by the asterisk).

Ultrasound

The pleura can be visualized on ultrasound imaging using a high-frequency, linear array probe (the same probe used for vascular ultrasound) that is placed across the intercostal spaces. The normal movement of the pleural surfaces creates a shimmering effect on the pleural image that is known as "lung sliding" (40). The absence of lung sliding then suggests the presence of a pneumothorax. Other conditions (e.g., blebs, pleurodesis) can be accompanied by the absence of lung sliding, so this sign is not pathognomonic of pneumothorax.

Several clinical studies have shown that ultrasound has a higher sensitivity than portable chest x-rays for the detection of pneumothoraces (36,37), including those associated with central venous cannulation (41). As a result, ultrasound has been recommended as a replacement for

chest radiography after central venous cannulation.

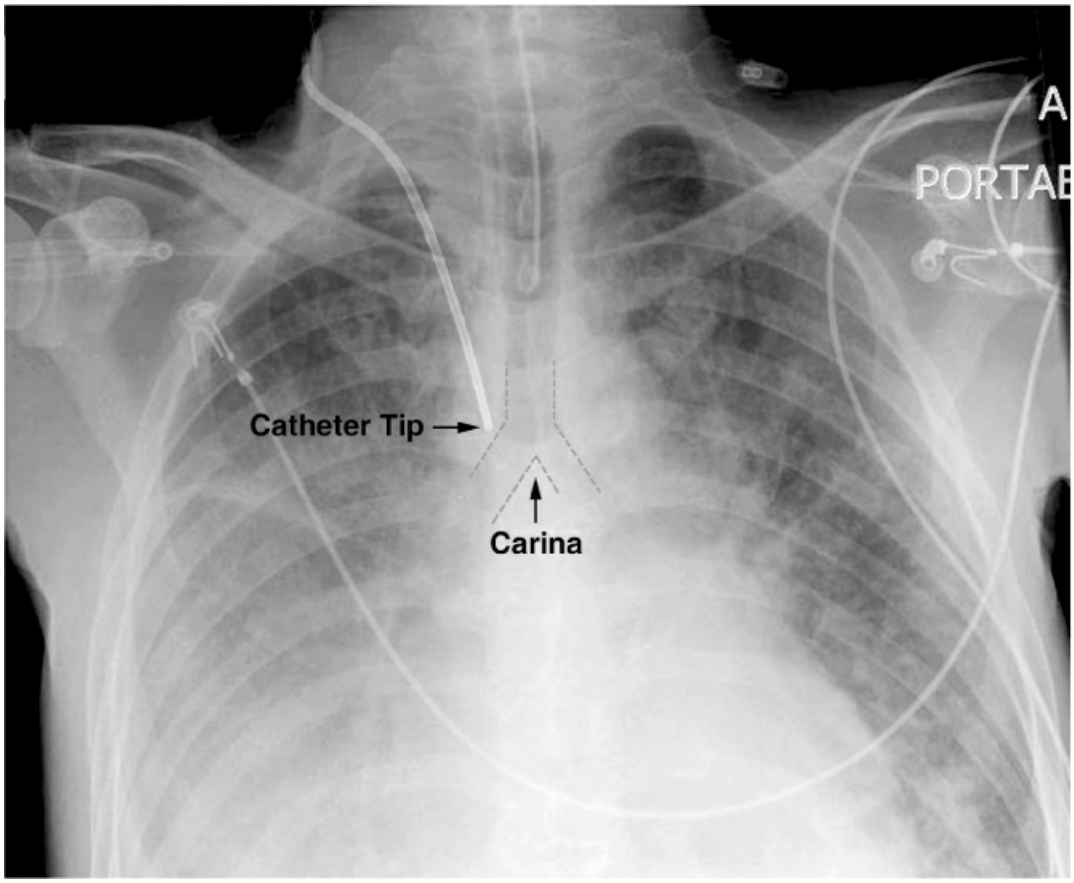

FIGURE 2.6 Portable chest x-ray showing the proper placement of a central venous catheter. Note that the tip of the catheter is at the level of the carina (i.e., the tracheal bifurcation, highlighted by the dotted lines), which lies just above the junction between the superior vena cava and right atrium. Image digitally enhanced

Catheter Position

Catheters inserted via the internal jugular and subclavian veins should be in the superior vena cava, with the tip 1–2 cm above the right atrium. Misplacement of catheters is reported in 15–18% of cannulations (41), mostly those involving the subclavian vein.

Chest Radiography

The standard practice is to evaluate catheter placement with a portable chest x-ray, and the one in Figure 2.6 shows a catheter that is appropriately placed. Note that the catheter follows a straight course down the mediastinum, and the tip of the catheter is just above the carina (i.e., the tracheal bifurcation). The carina is located just above the junction between the superior vena cava and the right atrium, so a catheter tip that is at the level of the carina, or slightly above it, is in the appropriate position. The carina is thus a useful landmark for evaluating catheter position (42).

Ultrasound

Ultrasound has been recommended as a replacement for chest radiography to evaluate catheter

placement. There are two aspects of the ultrasound examination. The first pertains to subclavian vein catheters, and involves imaging the internal jugular vein on both sides to identify cephalad misplacement of the catheter (which must be corrected). This can be done during the catheterization procedure to save time in repositioning the catheter.

The second aspect of the ultrasound exam uses a phased array transducer in the subcostal window to visualize the catheter in the right atrium. If the catheter is not in the right atrium, then a "bubble study" is performed. This involves the rapid injection of 10 ml of saline through the distal port of the catheter, and observing for the appearance of microbubbles in the right atrium. A positive test confirms that the catheter is in the venous system, while the appearance of the bubbles within 2 seconds of injection is evidence that the catheter tip is in the superior vena cava (43).

Catheter Tip in Right Atrium

Catheters that have been advanced into the right atrium have traditionally been repositioned because of the perceived risk of right atrial perforation and cardiac tamponade. However, this practice is being questioned because of the rarity of this complication (44). In one study that included 2,348 patients with a catheter tip that remained in the right atrium, there were no cases of cardiac perforation or troublesome cardiac arrythmias (45). As a result of studies like this, the practice of repositioning catheters that enter the right atrium is being abandoned.

A FINAL WORD

The following points related to central venous access deserve emphasis.

. The indications for central venous access are shrinking, thanks to the emergence of safer alternatives like midline catheters and peripherally inserted central catheters (PICCs).

. The use of real-time ultrasound improves the success rate, and reduces the complication rate, at all sites of central venous access.

. The perception that femoral vein catheters are particularly risky is not supported by clinical studies (see Table 2.2).

. Ultrasound is superior to portable chest radiography for detecting post-insertion pneumothoraces, and is a suitable alternative to chest radiography for evaluating catheter position.

. Catheters that have been advanced into the right atrium pose no great danger of cardiac perforation, and can be left in place.

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Chapter 3

The Indwelling Vascular Catheter

See, and then reason and compare and control. But see first.

Sir William Osler (*a*)

The ubiquitous presence of indwelling vascular catheters requires attention to their maintenance and vigilance for their troublesome complications. This chapter begins by describing the routine care and maintenance of indwelling catheters, including how to restore patency in an occluded catheter, and then focuses on the major complications of indwelling catheters: i.e., thrombosis, vascular perforation, and catheter-related infections.

ROUTINE CATHETER CARE

The considerations involved in routine catheter care are summarized in Table 3.1.

Protective Dressings

Catheter insertion sites should be covered with a sterile dressing for the life of the catheter. There are three types of dressings (1–3):

. Sterile gauze pads, which are secured to the skin with hypo-allergenic tape.

. Transparent polyurethane dressings, which are permeable to O_2, CO_2, and water vapor, but trap moisture that collects on the underlying skin. These dressings have a skin adhesive that produces a seal around the catheter insertion site, and they are commonly known as "occlusive" dressings.

. Chlorhexidine gluconate-impregnated sponge dressings, which can be placed over the catheter insertion site, and then covered with the transparent dressing.

The transparent occlusive dressings are favored because they allow routine inspection of the catheter insertion site, and also provide a seal that isolates the insertion site. However, the skin adhesive on these dressings does not work well when the skin is wet, so gauze dressings are preferred when the skin is difficult to keep dry. The chlorhexidine-impregnated dressings are typically available as a small sponge (e.g., Biopatch®) that is included in many central venous

catheter insertion sets.

Sterile gauze dressings and occlusive dressings are considered equivalent in preventing catheter colonization and infection (1–3). Chlorhexidine-impregnated dressings provide the best protection against catheter infections (1,2), but they are currently recommended only in settings where catheter-related infections are problematic (4).

TABLE 3.1 Recommendations for Routine Catheter Care

Task	Recommendations
Dressing Changes	Adhesive transparent dressings should be changed at least every 7 days, or (1) when moisture or blood accumulates under the dressing, or (2) the adhesive seal is disrupted. Gauze dressings should be changed at least every 48 hrs, or when the dressing is visibly soiled.
Flushing Catheters	Preservative-free 0.9% saline is preferred to heparinized saline for flushing venous catheters..
Replacing Catheters	Routine or scheduled replacement of catheters is not necessary, and can create complications.

Dressing Changes

The occlusive transparent dressings should be changed at least every 7 days, or when the adhesive seal is disrupted (2,3). In addition, *occlusive dressings can paradoxically promote colonization and infection when moisture or blood accumulates under the dressing* (5), and evidence of such should prompt a dressing change. Gauze dressings should be changed at least every 48 hours, or when the dressing is no longer dry (2,3).

Replacing Catheters

Routine or scheduled replacement of catheters is not advised (3) because it does not reduce the incidence of catheter-related infections (6), and actually increases the risk of catheter-associated complications (both mechanical and infectious) (7,8).

Peripheral Vein Catheters

Peripheral vein catheters are replaced when there is evidence of: (a) localized phlebitis (i.e., painful erythema around the insertion site, which can extend centrally along the course of the vein), (b) extravasation of the infusate, or (c) catheter obstruction that cannot be relieved (see later) (2). The phlebitis is typically the result of mechanical or chemical irritation of the target vessel, and does not represent infection (unless there is purulence emanating from the puncture site).

Central Venous Catheters

Central venous catheters are replaced when there is evidence of infection (either purulence at the insertion site or confirmed catheter-related septicemia). Catheter replacement is not necessary when there is erythema at the catheter insertion site without other signs of infection, since erythema alone is not predictive of catheter-related infection (9).

Flushing Catheters

Vascular catheters that are used intermittently are at risk of developing an occlusive thrombosis when not in use. To prevent this, the catheters are flushed at regular intervals, and the flush solution is left in the lumen of the catheter when it is not in use (known as "locking" the catheter). Flush solutions have traditionally contained heparin (in concentrations ranging from 10 to 1,000 units/mL, in isotonic saline), but these solutions are concerning because of the risk of heparin-induced thrombocytopenia (see Chapter 13). Isotonic saline has proven as effective as heparinized saline as a flushing and locking solution (10), and *preservative-free saline is now recommended as the preferred solution for flushing and locking venous catheters* (11). However, this is not the case for arterial catheters (12), where 1.4% sodium citrate is a suitable alternative to heparinized saline for maintaining catheter patency (13).

Occluded Catheters

Occlusion of indwelling vascular catheters is common, and can be the result of thrombus formation (60% of cases) mechanical factors (e.g., constriction from a suture), catheter malposition, or insoluble precipitates from drugs or minerals in the infusate (14). The occlusion can be partial or complete, and can appear as sluggish flow, loss of flow, or frequent triggering of alarms on infusion pumps (indicating excessive infusion pressures). Aspiration of blood through the catheter becomes difficult, or is not possible. (*Note:* Small-barrel syringes are preferred for aspiration through a catheter because they generate smaller negative pressures, and are less likely to collapse the lumen of the catheter.)

Restoring Patency

Short, peripheral vein catheters that become occluded are typically replaced, but for long catheters that are more difficult to replace (e.g., central venous catheters), every effort should be made to restore patency. Advancing a guidewire through the catheter to restore patency is not advised, since this can dislodge an obstructing mass and create an embolus. Chemical dissolution of the obstructing mass (described next) is the standard method of restoring patency.

THROMBOTIC OCCLUSION: Since thrombosis is the most common cause of catheter occlusion, the initial attempt to restore patency should involve the local instillation of a thrombolytic agent. Alteplase (recombinant tissue plasminogen activator) is currently the favored thrombolytic agent for restoring catheter patency; the regimen shown in Table 3.2 can restore patency in 80–90% of occluded catheters (15,16). There are 11 reports of angioedema associated with this regimen (17), and no reports of abnormal bleeding (16).

TABLE 3.2 Protocol for Declotting Central Venous Catheters

Drug	Alteplase (recombinant tissue plasminogen activator)
Preparation	Cathflo Activase (Genentech, Inc.) available as a powder in 2 mg vials. Add 2 mL sterile water to each vial for a drug concentration of 1 mg/mL.
Regimen	1. Instill 2 mL (2 mg) of drug solution into the occluded catheter and cap the hub of the catheter. 2. Wait 30 minutes and attempt to withdraw blood from the catheter.

	3. If the occlusion persists, wait another 90 minutes (total dwell time = 120 min) and attempt to withdraw blood from the catheter. 4. If the occlusion persists, prepare a second dose of alteplase (2 mg) and repeat steps 1–3. 5. If patency is restored, withdraw 5 mL of blood through the catheter to remove any residual clot. 6. If this regimen does not restore patency, consider the non-thrombotic sources of obstruction in Table 3.3.

From Reference 16.

TABLE 3.3 Non-Thrombotic Catheter Occlusion

Etiology	Treatment	Regimen
Alkaline Drug Precipitates		1. Instill 1 mL or catheter lumen volume. 2. Dwell 60 minutes 3. Attempt flushing with 10–20 mL 0.9% saline. 4. Repeat if needed.
acyclovir, ampicillin diazepam, gancyclovir heparin, imipenem phenytoin	$NaHCO_3$ (8.4%) or NaOH (0.1 mmol/L)	
Acidic Drug Precipitates		
calcium gluconate, ceftriaxone, PN mixtures, vancomycin	HCL (0.1 N) or L-cysteine (50 mg/mL)	
Mineral Precipitates		
PN mixtures rich in Ca^{++} and PO_4^-	NaOH (0.1 N) for first attempt, then L-cysteine (50 mg/mL)	
Lipid or Protein Residues		
PN mixtures, Propofol	ETOH (70%) for lipids NaOH (0.1 N) for lipids and proteins	1. Instill 10 mL over 60 min. 2. Dwell for 2 hrs. 3. Attempt flushing with 10–20 mL 0.9% saline. 4. Repeat if needed.

From References 11 and 14. ETOH = ethanol, HCL = hydrochloric acid, NaHCO3 = sodium bicarbonate, NaOH = sodium hydroxide, PN = parenteral nutrition.

NON-THROMBOTIC OCCLUSION: Failure of the thrombolytic regimen to restore patency should prompt consideration of the non-thrombotic causes of catheter occlusion shown in Table 3.3. Note that alkaline precipitates are cleared with an alkaline solution (sodium bicarbonate or sodium hydroxide) and acidic precipitates are cleared with an acid (hydrochloric acid), while lipid residues can be cleared with 70% ethanol (11,14).

NON-INFECTIOUS COMPLICATIONS

The non-infectious complications of indwelling catheters include catheter-related venous thrombosis and vascular perforation.

Catheter-Related Thrombosis

Indwelling catheters can trigger localized thrombus formation by injuring the vascular endothelium, or by platelet adhesion to the catheter. Catheter-related thrombosis is especially prevalent with peripherally inserted central catheters (PICCs), but the thrombosis is clinically silent in more than 95% of cases (18). There is an increased risk of catheter-related thrombosis in cancer patients, especially those with long-term, tunneled catheters for chemotherapy (19).

Upper Extremity Thrombosis

Deep vein thrombosis (DVT) is not limited to the lower extremities; i.e., about 5% of cases involve the deep veins above the elbow (19,20), and as many as 90% of these are attributed to the presence of a catheter (e.g., a midline catheter or PICC) (20). The other risk factor for this type of DVT is malignancy; i.e., one-quarter to one-third of patients with upper extremity DVT have an active malignancy (19).

Upper extremity DVT can be clinically silent, and the only consequence may be difficulty aspirating blood through the involved catheter. Complete thrombotic obstruction eventually produces swelling of the upper arm, which can be accompanied by discomfort, paresthesias, arm weakness, and engorgement of the superficial veins around the shoulder (Urschel's sign!) (19). The thrombosis can also propagate into the superior vena cava, but the *superior vena cava syndrome* (with facial swelling, headache, etc.) is a rare consequence of catheter-associated DVT (21). Finally, fewer than 10% of upper extremity DVTs are associated with symptomatic pulmonary emboli (22).

DIAGNOSIS: Compression ultrasonography is the diagnostic test of choice for upper extremity DVT (see Figure 1.7 for a normal compression test). A positive test (i.e., clot-filled veins are not compressible) has s sensitivity of 97% and a specificity of 96% for upper extremity DVT (19). D-dimer levels are not reliable as a screening test for DVT because critically ill patients often have elevated D-dimer levels.

MANAGEMENT: Removal of the offending catheter is not mandatory in upper extremity DVT, and is recommended only when arm swelling is severe or painful, or when anticoagulant therapy is contraindicated (19,20). The anticoagulant regimens used for lower extremity DVT have been adopted for the upper extremity. These regimens are described in Chapter 22.

Lower Extremity Thrombosis

Femoral vein catheters are considered high-risk for catheter-related thrombosis, especially when left in place for several days. However, the reported incidence of symptomatic DVT with these catheters is only 1.6% (23), and there is no documented correlation between the duration of catheter use and the appearance of DVT (23). Therefore, the risk of DVT with these catheters is overstated.

Vascular Perforation

Perforation of the superior vena cava or right atrium is an uncommon but potentially life-threatening complication of central venous cannulation. This complication is also avoidable with vigilance for malpositioned catheters.

Superior Vena Cava Perforation

Left-sided central venous catheters that are advanced into the superior vena cava (SVC) do not always make the acute turn downward toward the right atrium. When this occurs, the tip of the catheter abuts the lateral wall of the SVC, as shown in the upper chest x-ray in Figure 3.1. If the catheter remains in this position, the tip of the catheter can erode through the vessel wall, resulting in leakage of blood and intravenous fluids into the mediastinum and pleural space. The symptoms from SVC perforation i.e. (substernal chest pain, cough, and dyspnea) are nonspecific, and suspicion of perforation is often prompted by the sudden appearance of mediastinal widening and a pleural effusion on the chest x-ray, like the lower x-ray in Figure 3.1 (24).

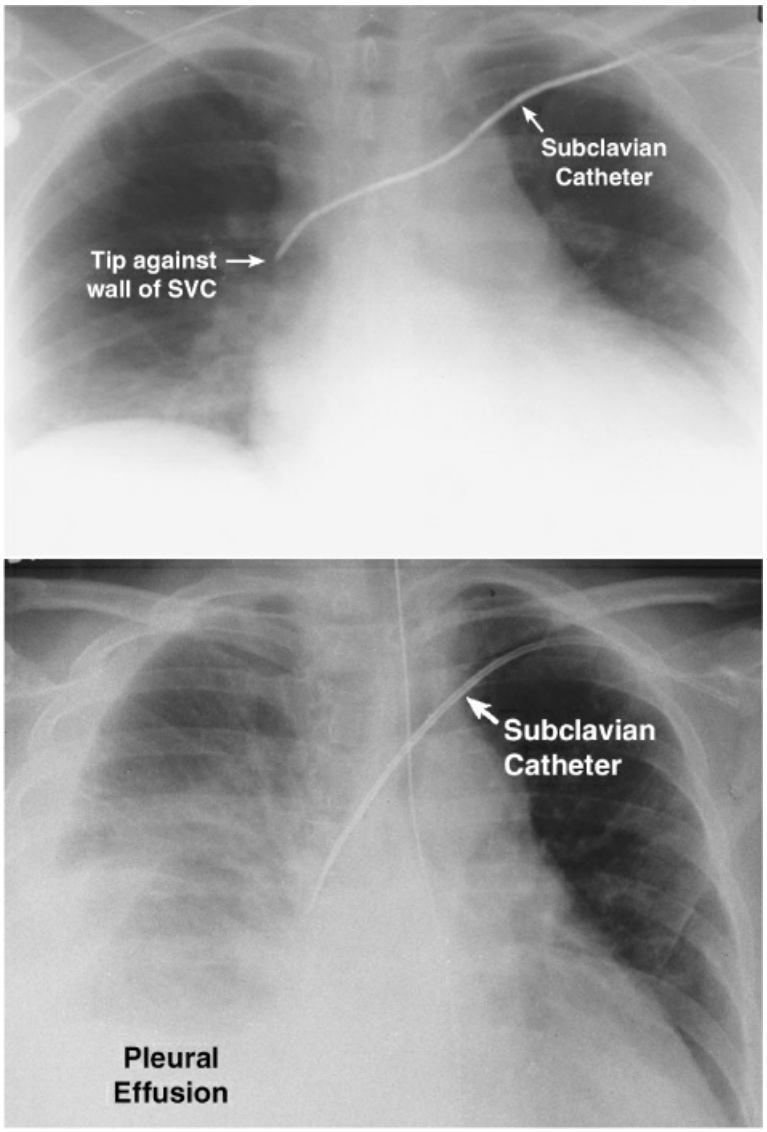

FIGURE 3.1 Chest x-rays showing a subclavian vein catheter that is positioned to perforate the superior vena cava (upper panel), and a similarly positioned catheter that has perforated the vena cava (lower panel). Lower chest x-ray from Reference 24.

DIAGNOSIS: The pleural effusions can be largely composed of intravenous fluids that escape through the perforation; as such, a thoracentesis can support the diagnosis of SVC perforation if the pleural fluid is similar in composition to the intravenous infusion fluid. The perforation is confirmed by injecting radiocontrast dye through the catheter and noting the presence of dye in the mediastinum or pleural space.

MANAGEMENT: When vena cava perforation is first suspected, infusion through the catheter should be stopped immediately. If the diagnosis is confirmed, the catheter should be removed (this does not provoke mediastinal bleeding) (24). Antibiotic therapy is not necessary unless there is evidence of infection in the pleural fluid (24).

Cardiac Tamponade

The most life-threatening complication of central venous catheters is cardiac tamponade from a catheter tip that perforates the right atrium. Fortunately, this complication is rare (see References 44 and 45 in Chapter 1). The first sign of tamponade is usually the abrupt onset of dyspnea, which can progress to cardiovascular collapse within an hour. The diagnosis requires ultrasound evidence of a pericardial effusion with diastolic collapse of the right heart, and immediate pericardiocentesis is necessary to reduce the pericardial pressure and allow the right heart to fill. Emergency thoracotomy may also be necessary if there is a large tear in the wall of the heart. The mortality rate in this condition varies from 40% to 100% in published reports (25).

CATHETER-RELATED BLOODSTREAM INFECTIONS

Indwelling vascular catheters (with the exception of short, peripheral vein catheters) are the leading source of nosocomial bloodstream infections, and septicemia from indwelling catheters has a mortality rate of 12–25% in ICU patients (26,27). The average rate of infections involving central venous access catheters is 4.6 per 1,000 catheter days (28).

Pathogenesis

Colonization of indwelling vascular catheters has several potential sources, as indicated in Figure 3.2. Each of these sources is described below using the corresponding numbers in the illustration.

. Microbes can gain access to the bloodstream via contaminated infusates (e.g., blood products), but this occurs rarely.

. Contamination of the internal lumen of vascular catheters can occur through break points in the infusion system, such as catheter hubs. This may be a prominent route of infection for catheters inserted through subcutaneous tunnels.

. Microbes on the skin can migrate along the subcutaneous tract of an indwelling catheter. This is considered the principal route of infection for percutaneous (non-tunneled) catheters, which includes most of the catheters used in the ICU. (For a novel view concerning this route of

infection, see A FINAL WORD at the very end of the chapter).

. Microorganisms in circulating blood can attach to the intravascular portion of the catheter. The catheter is not considered the primary source of infection in this situation, but it is possible that the proliferation of the microbes on the catheter reaches a point where the catheter becomes a source of bacteremia.

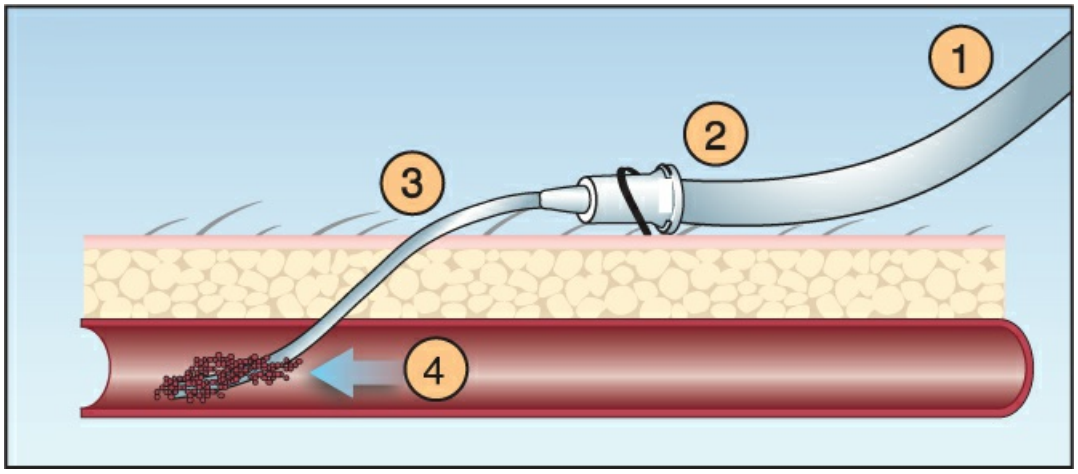

FIGURE 3.2 Sources of microbial colonization of intravascular catheters. See text for explanation.

Biofilms

Microbes have a propensity to congregate on inert surfaces. Once in contact with a surface, they releases adhesive molecules (called *adhesins*, of course) that firmly attach them to the surface. They then begin secreting an extracellular matrix (known as *slime*) that consists of polysaccharides, proteins, fibrin, and extracellular DNA (29). This extracellular matrix creates a protective environment called a *biofilm* that allows microbes to thrive and proliferate without being damaged by the surrounding environment. Phagocytic cells are unable to ingest organisms that are embedded in a biofilm, and *antibiotic concentrations that eradicate free-living bacteria must be 100 to 1,000 times higher to eradicate bacteria in biofilms* (30).

Biofilms are ubiquitous in nature, and predominate on surfaces that are exposed to moisture. (The slippery film that covers rocks in a stream is a familiar example of a biofilm.) They also form on indwelling medical devices such as endotracheal tubes, urinary catheters, and vascular catheters, and can be found on biological surfaces such as the oral mucosa, the epithelial surface in the airways, the mucosal lining of the GI tract, and the surface of native heart valves.

CATHETER-RELATED INFECTIONS: Biofilms play an important role in catheter-related infections, as shown by the following observations:

. Examination of indwelling vascular catheters with scanning electron microscopy has revealed extensive biofilm formation on the surface of the catheters, including those that were in place for only one day (31).

. Coagulase-negative staphylococci, which are the leading cause of catheter-related infections, readily adhere to polymer surfaces and produce slime (32). A biofilm of *Staphylococcus*

epidermidis is shown in Figure 3.3.

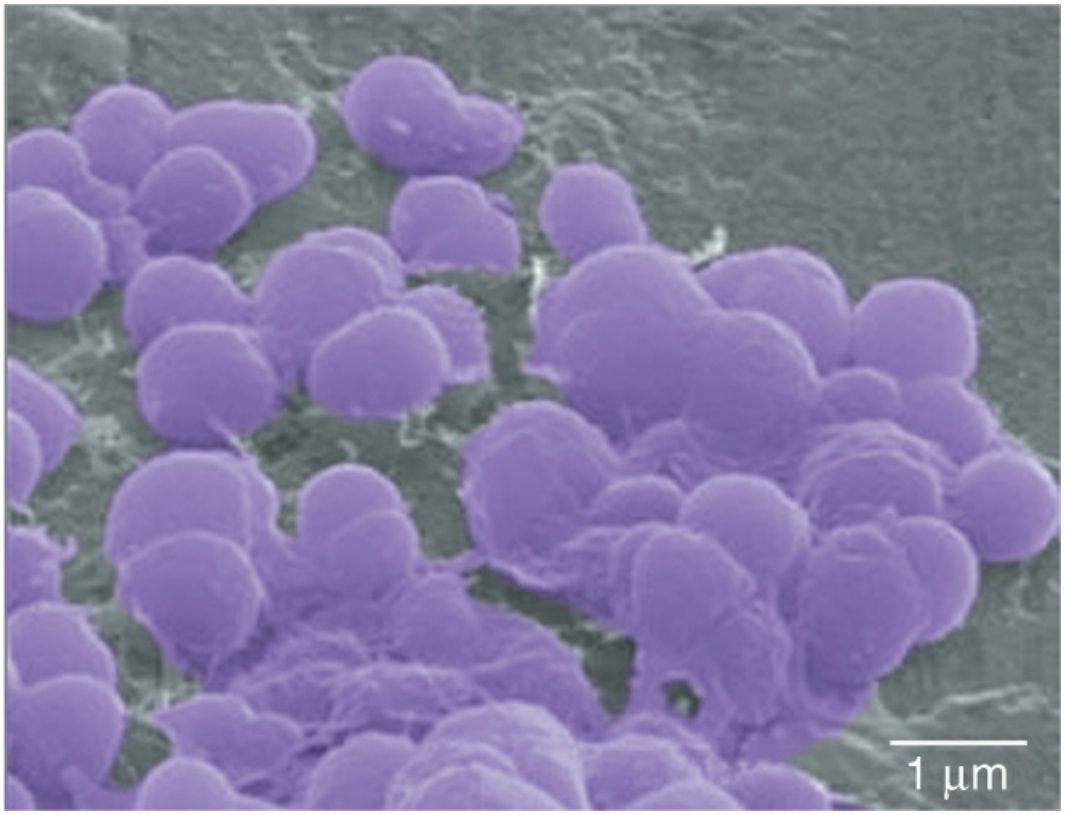

FIGURE 3.3 Electron micrograph of *Staphylococcus epidermidis* encased in a biofilm. Image courtesy of Jeanne VanBriesen, Ph.D., Carnegie Mellon University. Image colorized digitally.

The ubiquitous presence of biofilms on indwelling vascular catheters means that antibiotic therapy is not the optimal treatment for catheter-related bloodstream infections. (The doses of antibiotics needed to achieve bactericidal levels in biofilms would be toxic to the host.) Several anti-biofilm strategies are being evaluated (33), but nothing has reached clinical testing at this time.

Clinical Features

Catheter-related infections do not appear in the first 48 hours after catheter insertion (which presumably is the time required for colonization of the catheter tip). When they do appear, the clinical manifestations are non-specific: e.g.,

. Fever and leukocytosis are common manifestations, but these are signs of inflammation, and are not evidence of infection.

. There may be erythema around the catheter insertion site, but this has no predictive value for identifying catheter-related infections (9).

. Purulent drainage from the catheter insertion site is evidence of infection, but it can be an exit-site infection, without invasion of the bloodstream (34).

Because of the non-specific nature of these clinical findings, the diagnosis of catheter-related infections is not possible on clinical grounds.

Diagnosis

The diagnosis of catheter-related septicemia requires a positive blood culture from a site other than the catheter, plus some evidence that the catheter is the source of the positive blood culture (and is not secondarily seeded). This evidence was originally provided by a semiquantitative culture of the catheter tip, but this method fell from favor because it required removal of the catheter (which is not desirable, because many cases of suspected catheter-related infection are not confirmed), and the outer surface of the catheter was cultured, thereby missing infections arising from the lumen(s) of the catheter. The culture methods that are currently recommended are summarized in Table 3.4 (35,36).

TABLE 3.4 Recommended Culture Methods for the Diagnosis of Catheter-Related Septicemia

Culture Method	Diagnostic Criteria
Differential Quantitative Blood Cultures	Same organism in peripheral blood & catheter blood, and colony count from catheter blood ≥3 times greater than colony count from peripheral blood. (Accuracy = 94%)[1]
Differential Time to Positive Cultures	Same organism in peripheral blood & catheter blood, and onset of growth in catheter blood at least 2 hours before onset of growth in peripheral blood. (Accuracy = 91%)[1].

From the clinical practice guidelines in Reference 34.

[1] From Reference 37.

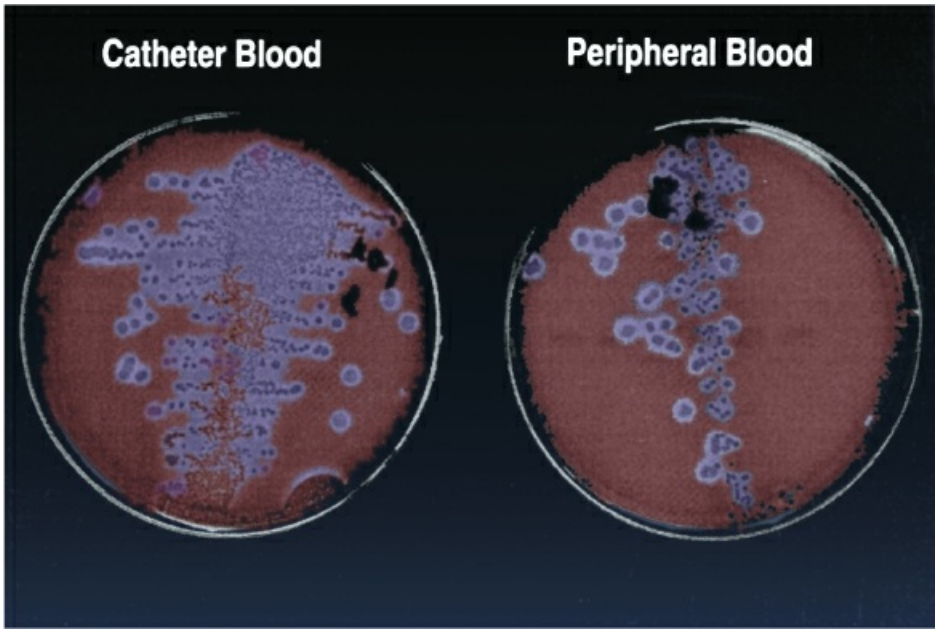

FIGURE 3.4 Culture plates from a case of catheter-related septicemia showing denser growth in blood drawn through a central venous catheter *(Catheter Blood)* compared to blood from a

peripheral venipuncture *(Peripheral Blood)*. From Reference 36. Image colorized digitally.

Quantitative Culture Method

This method uses paired blood cultures (one drawn through the catheter, and one from a peripheral venipuncture site), and is based on the expectation that if the catheter is the source of a bloodstream infection, blood drawn through the catheter will have a higher growth density than the peripheral blood. This requires a "quantitative" blood culture, where growth is expressed as the number of colony forming units per mL (like urine cultures). The diagnosis of catheter-related infection is confirmed if the same organism is isolated from catheter blood and peripheral blood, and the colony count in catheter blood is at least 3 times greater than the colony count in peripheral blood. An example of the comparative growth density in a case of catheter-related septicemia is shown in Figure 3.4.

Timed Culture Method

This method also uses paired blood cultures (one drawn through the catheter, and one from a peripheral venipuncture site), and is based on the expectation that if the catheter is the source of a bloodstream infection, the blood withdrawn through the catheter will show microbial growth at an earlier time than peripheral blood. This method uses routine (qualitative) blood cultures, and the diagnosis of catheter-related infection is confirmed if the same organism is isolated from the catheter blood and peripheral blood, and growth is detected at least 2 hours earlier in the catheter blood.

Which Method is Preferred?

Neither method is clearly superior to the other. The quantitative method has a sightly higher accuracy (37), but the difference is small (94% versus 91%), and may not justify the higher cost of the quantitative method. There is actually little enthusiasm for either culture method, and the diagnosis of catheter-related infection is often based on the same organism being isolated in catheter blood and peripheral blood, with no other apparent source of infection.

HOW MANY LUMENS TO CULTURE? Central venous catheters typically have three lumens (and can have four) and each lumen is a potential source of septicemia (38). However, the recommended practice is to obtain catheter-derived blood cultures from a single lumen (34). The problem with this practice is highlighted by a study showing that *38% of catheter-related infections would be missed if single-lumen cultures were used in the diagnostic evaluation* (39). Using a pooled blood culture from all lumens (to reduce the volume of blood needed to culture multiple lumens) has not proven to be as sensitive as cultures from each lumen (40). At the present time, the available evidence indicates that *the diagnostic approach to catheter-related infection is optimal when blood cultures are drawn through each lumen of the catheter*.

TABLE 3.5 The Top Ten Pathogens in Catheter-Related Septicemia

1–5	6–10
1. Coag-negative staphylococci (16%)†	6. *Candida albicans* (6%)
2. *Staphylococcus aureus* (13%)	7. *Escherichia coli* (5.4%)

3. *Enterococcus faecalis* (8.4%)	8. Other *Candida* spp. (5%)
4. *Klebsiella pneumoniae* (8.4%)	9. *Enterobacter* spp. (4.4%)
5. *Enterococcus faecium* (7%)	10. *Pseudomonas aeruginosa* (4%)

†Numbers in parentheses represent percentage of all isolates.
From Reference 41.

Management

Empiric antibiotics are recommended for all ICU patients with suspected catheter-related infection, and they should be started immediately after cultures are obtained. The pathogens that are most frequently involved in catheter-related infections are shown in Table 3.5. This list is from the National Healthcare Safety Network (41), and it represents the summed contribution of 4,515 hospitals. Note that staphylococci and enterococci together account for 45% of all offending pathogens.

Empiric Antibiotic Therapy

The recommendations for empiric antibiotic coverage are shown in Table 3.6. Van comycin is the backbone of the empiric regimen because it is the most active agent
against staphylococci (including coagulase-negative and methicillin-resistant strains),
and enterococci. Daptomycin can substitute for vancomycin if there is evidence of van comycin-resistance. Empiric coverage for gram-negative enteric organisms is advised for neutropenic or seriously ill patients (35); suitable antibiotics include the carbapenems (e.g., meropenem), the fourth-generation cephalosporins (e.g., cefepime), and the β-lactam/β-lactamase inhibitor combinations (e.g., piperacillin/tazobactam). Additional gram-negative coverage (with an aminoglycoside) is recommended when multidrug-resistant gram-negative organisms are possible offenders

Empiric coverage for candidemia is recommended when the conditions listed in Table 3.6 are present. The echinocandins (caspofungin, micafungin, and anidulafungin) are more active than the azoles (e.g., fluconazole) against all *Candida* species and thus are favored for empiric antifungal coverage (35).

Catheter Management

As mentioned earlier, most cases of suspected catheter-related infections are not con firmed by culture results: e.g., in one study, 1,527 catheters were removed for suspected catheter-related infection, and the diagnosis was confirmed in only 169 (11%) of the cases (28). Therefore, catheters should be left in place pending culture results.

TABLE 3.6 Empiric Antibiotic Coverage for Common Pathogens in Catheter-Related Infections

Organism	Antibiotic	Comment
Staphylococci	Vancomycin	If MRSA isolates with MIC >2 mg/mL are prevalent, use daptomycin..
Enterococci	Vancomycin	If vancomycin resistance is a concern, use daptomycin.

Gram Negative Bacilli	Carbapenem[a] or Cefepime or Piperacillin-Tazobactam	Add aminoglycoside for neutropenia or concern for multidrug-resistant organisms.
Candida species	Echinocandin[b]	***Indications:*** Femoral catheter, TPN, hematologic malignancy, prolonged antibiotic Rx, recent transplant, or *Candida* spp. elsewhere.

From References 34,35.

[a]Carbapenems include imipenem, meropenem, and doripenem.

[b] Echinocandins include caspofungin, micafungin, and anidulafungin.

INDICATIONS FOR CATHETER REMOVAL: If the diagnosis of catheter-related infection is confirmed, catheters should be removed if any of the following is present:

. Hemodynamic instability or progressive multiorgan dysfunction.

. Evidence of endocarditis or septic thrombophlebitis.

. Infections with *Staphylococcus aureus, Candida* species, *Pseudomonas* species, or multidrug-resistant gram-negative bacilli.

. Persistent bacteremia for >96 hrs despite appropriate antimicrobial therapy.

Catheters should not be replaced over a guidewire, but instead should be removed and reinserted at a new venipuncture site. However, guidewire replacement may be the best option if there is very limited venous access.

There is an increasing tendency to leave catheters in place, because inserting a new catheter is time consuming, costly, and can be risky. Even guidewire exchanges can have complications (7). When a catheter is left in place, systemic antibiotics will have limited or no efficacy in decontaminating the catheter (because of the biofilm on the catheter), and recurrent infections are expected (42). In this situation, antibiotic lock therapy should be considered.

ANTIBIOTIC LOCK THERAPY: Instilling concentrated antibiotic solutions into indwelling catheters and allowing an extended dwell time will enhance the ability to disrupt biofilms and eradicate persistent organisms (35). The antibiotic "lock" solution contains the same antibiotic used systemically, in a concentration of 2–5 mg/mL in heparinized saline. This solution is injected into each lumen of the indwelling catheter and allowed to dwell for 24 hours, and is replaced every 24 hours for the duration of the systemic antibiotic therapy. If the catheter is never idle and antibiotic lock therapy is not possible, the systemic antibiotic(s) should be delivered through the suspect lumen.

Duration of Antimicrobial Treatment

The duration of antibiotic therapy is determined by several factors, including the offending pathogen, the status of the catheter (i.e., replaced or retained), and the response to antimicrobial therapy. The following are some general suggestions (34):

. If the infection involves a microbe with limited pathogenicity (e.g., coagulase-negative staphylococci), and there is a favorable response to antimicrobial therapy within 72 hours, then

no more than 7 days of treatment is necessary (34).

. For cases of *Staph aureus* bacteremia, the accepted practice is to look for evidence of endocarditis with transesophageal ultrasound (the rationale for this is stated later). If there is no evidence of endocarditis, antibiotic therapy can be limited to 14 days if the following conditions are satisfied: the catheter has been removed, the patient is not immunocompromised, and there are no intravascular prosthetic devices in place (34). Evidence of endocarditis mandates 4–6 weeks of antimicrobial therapy, and an infectious disease consult.

. For infections caused by enterococci or gram-negative bacilli, 7–14 days of antibiotic therapy is advised, regardless of whether the catheter is replaced or retained (34).

Persistent Sepsis

Continued signs of sepsis or persistent septicemia after 72 hours of antimicrobial therapy should prompt a search for the following conditions.

Suppurative Thrombophlebitis

The thrombi that form around indwelling vascular catheters can trap microbes from a colonized catheter. These microbes can then proliferate (since blood is a good culture medium) and transform the thrombus into an intravascular abscess. This condition is known as *suppurative thrombophlebitis*, and the most common offending organism is *Staphylococcus aureus* (34). Clinical manifestations are often absent, but can include purulent drainage from the catheter insertion site, limb swelling from thrombotic venous occlusion, and multiple cavitary lesions in the lungs from septic emboli.

The diagnosis of septic thrombophlebitis requires evidence of thrombosis in the cannulated blood vessel (by ultrasound) and persistent septicemia with no other apparent source. Treatment includes catheter removal and systemic antibiotic therapy for 4–6 weeks (2). Surgical excision of the infected thrombus is usually not necessary, and is reserved for cases of refractory septicemia. There is no consensus on the use of heparin anticoagulation in suppurative thrombophlebitis, and current guidelines (34) recommend that heparin therapy should be considered.

Endocarditis

Nosocomial endocarditis is uncommon, with the reported incidence in university teaching hospitals being 2–3 cases annually (43,44). Vascular catheters are implicated in 30 to 50% of cases, and staphylococci (mostly *S. aureus*) are the offending organisms in up to 75% of cases (43,44). Methicillin-resistant strains of *S. aureus* (MRSA) predominate in some reports (45).

Typical manifestations of endocarditis (e.g., new or changing cardiac murmur) can be absent in as many as two-thirds of patients with nosocomial endocarditis involving *Staphylococcus aureus* (45), which is why a search for endocarditis (with transesophageal ultrasound) is advised for all patients with *S. aureus* bacteremia.

A FINAL WORD

A Novel View of Catheter-Related Infections

One of the core beliefs in critical care is the notion that catheter-related bloodstream infections are caused by skin microbes that travel down the tract of the catheter and colonize the distal end of the catheter. This paradigm for catheter-related infections is rarely questioned, yet there are a number of observations that do not fit the model. The following observations suggest that the skin is *not* the source of catheter colonization and infection.

. There is a poor correlation between the organisms found on the skin at the catheter insertion site, and the organisms found on the distal end of central venous catheters (46).

. Decontamination of the catheter insertion site with antibiotic ointments does not reduce the incidence of catheter-related bloodstream infections (3).

. The shortest route for skin microbes to enter the bloodstream is via peripheral vein catheters, which sit in superficial veins, yet these catheters are rarely implicated as a cause of catheter-related septicemia.

The next set of observations suggest that the bowel is the source of catheter-related infections:

. Gram-negative bacilli, enterococci, and *Candida* species account for about half of the microbes that are responsible for catheter-related infections (see Table 3.5), and these organisms are inhabitants of the bowel, not the skin.

. In cases of catheter-related infections, cultures of the upper GI tract show a better correlation with catheter tip cultures than cultures of the skin around the catheter insertion site (47).

. Decontamination of the bowel with nonabsorbable antibiotics has been shown to markedly reduce the incidence of catheter-related infections, and in some studies, these infections were completely abolished by bowel decontamination (48).

The prominence of staphylococci in catheter-related infections does not eliminate the bowel as a source of these infections because staphylococci are prominent inhabitants of the bowel during prolonged antibiotic therapy (49), and in critically ill patients (50). In fact *Staphylococcus epidermidis* (the leading cause of catheter-related infections) *is one of the most prevalent organisms in the upper GI tract of patients with multiorgan failure* (50). The species name *epidermidis* is thus a misnomer, since these organisms do not exclusively inhabit the epidermis.

The catheters that are responsible for catheter-related infections are lengthy (i.e., 6 to 12 inches for central venous catheters, and 15 to 20 inches for peripherally inserted central catheters) and the long intravascular segments of these catheters may be prone to seeding during occult or transient bacteremias. Once seeded, microbial proliferation on the catheter could reach the point where the catheter seeds the bloodstream, creating the appearance of a primary catheter-related bloodstream infection. Seeding of the catheters with bowel organisms is very possible, because the bowel is considered a prominent source of occult sepsis in critically ill patients (50). (See Chapter 4.)

Why does this matter? Because if the skin is not the site of origin for catheter-related infections, then we are spending a lot of time and money decontaminating the wrong surface.

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Section II

COMMON PRACTICES

We think so because all other people think so;
or because we think we in fact do think so;
or because we were told to think so and think we must think so;
or because we once thought so and think we must think so
or because of having thought so, we think we must still think so.

Henry Sidgwick
(1838–1900)

Chapter 4

Alimentary Prophylaxis

We are told the most fantastic biological tales. For example, that it is dangerous to have acid in your stomach.

JBS Haldane (1939)

Antiseptic practices are focused almost exclusively on the skin, but there is another, even larger surface that can be breached by microbes: i.e., the mucosal lining of the gastrointestinal (GI) tract. The lumen of the GI tract is outside the body (like the hole in a donut), and the mucosal surface serves as a barrier to microbial invasion, just like the skin. However, the skin is a multilayer affair with a keratinized covering, while the GI mucosa (our "inner skin") is a single layer of columnar epithelial cells that is only 0.1 mm thick, and serves as a barrier for an estimated 100 to 400 *trillion* microbes that inhabit the bowel (1). This scenario of a paper-thin barrier for an enormous army of microbes highlights the threat of microbial invasion from the bowel.

This chapter will introduce you to the importance of the alimentary tract (which extends from the oral cavity to the rectum) as a source of infection in critically ill patients, and describes the antiseptic measures that are available for this site. Also included is a section on stress-related mucosal injury in the stomach, and what can be done to prevent troublesome bleeding from this condition.

MICROBIAL INVASION FROM THE BOWEL

The Intestinal Microbiome

Bacteria are aquatic in nature, and the moisture-rich environment in the alimentary tract is ideal for microbial proliferation. The GI tract is home to about 70,000 distinct bacterial genomes (2), with an estimated population of 100 – 400 × 10^{12} organisms (1), and a total mass of about 2 kg (4.4 pounds) (3). The distribution of this mass is not uniform, as depicted in Figure 4.1 (4). Note that the stomach is the least populated region of the alimentary tract, with fewer than 1,000 organisms per mL of gastric secretions. Overall, about 99% of the microorganisms in the GI tract are located in the large bowel.

The microbial population in the bowel is present almost from birth (presumably introduced in the mother's milk), and it functions as a collective "ecosystem" that is known as a *microbiome*. The intestinal microbiome is protected from invaders by the actions of gastric acid, which eradicates pathogens ingested in contaminated food products (e.g., *Salmonella* spp), or transmitted via the fecal-oral route (e.g., *Clostridium difficile*). (The antimicrobial actions of gastric acid are described later.)

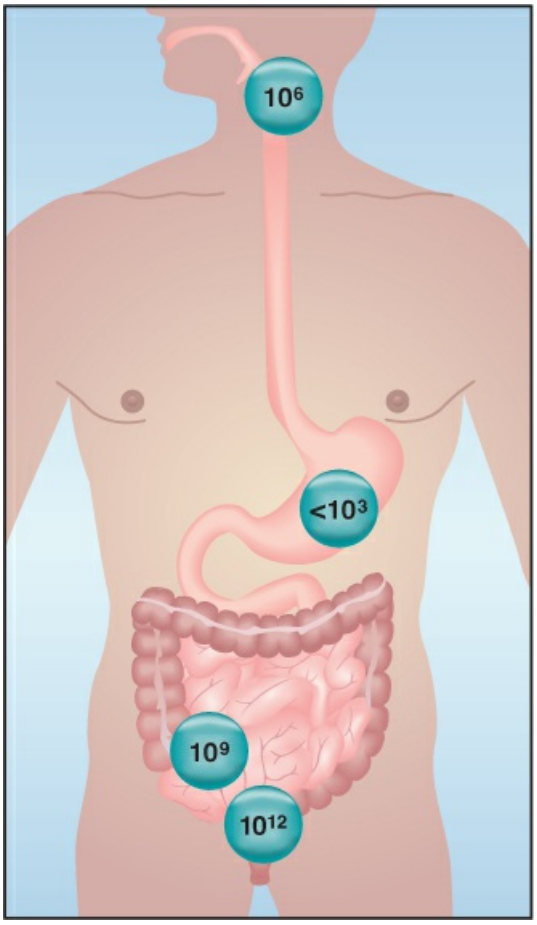

FIGURE 4.1 The population density of microorganisms in different regions of the alimentary tract. Numbers indicate colony forming units per mL of luminal contents. (From Reference 4).

Protective Effects

The intestinal microbiome has a symbiotic relationship with the host organism, and is instrumental in protecting against microbial invasion from the bowel. This is achieved by the following mechanisms (2,5):

. Resident microbes prevent colonization with pathogenic organisms by attaching to the intestinal mucosa and occupying all available spaces.

. Microbial production of short-chain fatty acids provides essential fuels for the mucosal cells in the bowel, which helps to maintain the mucosal barrier.

. Microbial products contribute to the proper functioning of the gut-associated lymphoid tissue

(GALT) which traps and destroys microbes that breach the mucosal barrier (6).

Disruption of the microbiome, a condition known as *dysbiosis*, impairs each of these mechanisms and promotes pathogenic invasion from the bowel. This is illustrated in Figure 4.2. The movement of pathogens across the bowel wall is known as *translocation* (7), and it is a principal source of sepsis and multiorgan failure in critically ill patients.

Multiorgan Failure

The leading cause of death in critically ill patients is multiorgan failure (8), a condition characterized by systemic inflammation (fever, leukocytosis, etc.) that persists or progresses, and is accompanied by progressive dysfunction in two or more major organs (9). The bowel is believed to be the source of this life-threatening condition (10), as described next.

The Motor of Multiorgan Failure

The inciting event in multiorgan failure can be a derangement of the intestinal microbiome (dysbiosis), or a period of splanchnic hypoperfusion. Both conditions lead to disruption of the gut mucosal barrier, which then permits enteric pathogens and/or proinflammatory mediators to gain access to the systemic circulation. This initiates a systemic inflammatory response (e.g., fever, leukocytosis), which is accompanied by hemodynamic changes (i.e., sympathetic nervous system activation with splanchnic vasoconstriction) that promotes further disruption of the gut mucosal barrier, and so on. The result is a self-sustaining process that continually drives systemic inflammation, and eventually produces inflammatory injury in multiple organs. According to this scenario (and to borrow a popular phrase), *the bowel is the 'motor' of multiorgan failure* (10).

Gastric Acid as an Antiseptic Agent

Gastric acid is often misperceived as a digestive aid. Although an acid environment in the stomach does facilitate the absorption of iron and calcium, patients with achlorhydria (the absence of gastric acidity) are not troubled by nutrient malabsorption. As mentioned earlier, *the principal function of gastric acid is not to facilitate digestion, but to serve as an antimicrobial defense against ingested pathogens* (11). The antimicrobial value of acids has been known since the introduction of antiseptic medicine (see next).

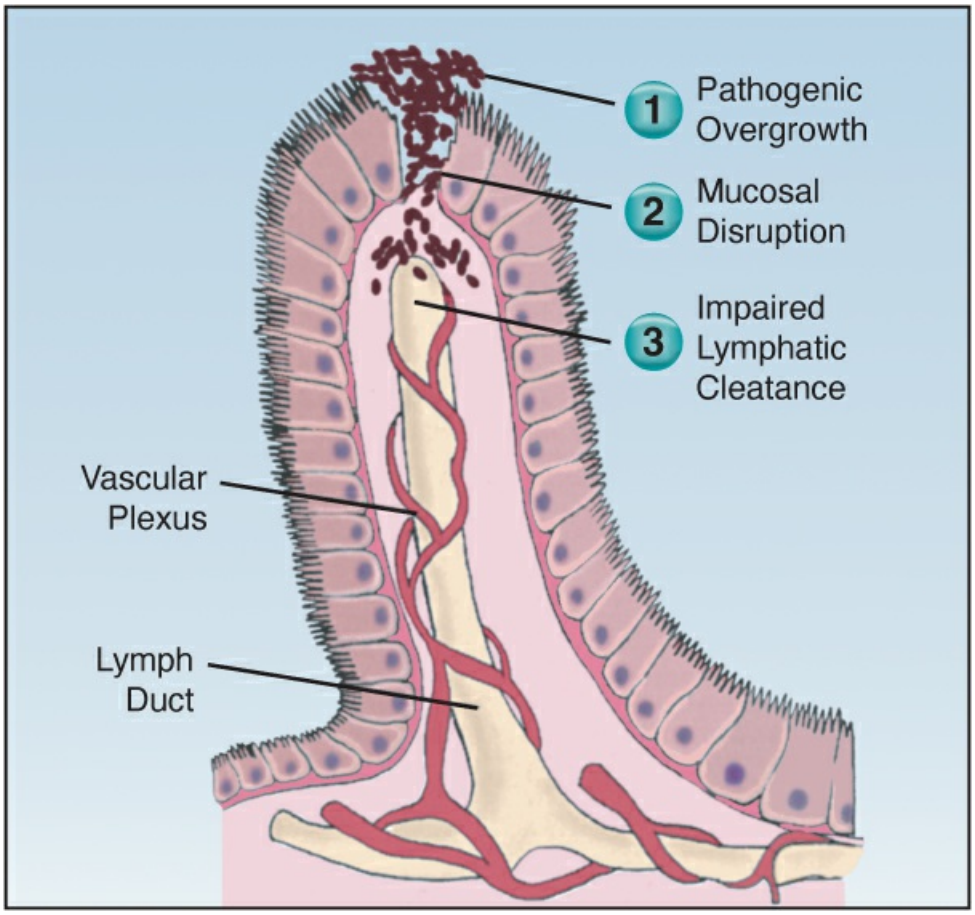

FIGURE 4.2 Consequences of disrupting the intestinal microbiome, which promotes the invasion of pathogens from the bowel.

Historical Note

The benefits of antisepsis were first recognized in the mid-nineteenth century by a British surgeon named Joseph Lister, who discovered that a chemical agent used to treat sewage could also reduce the number of suppurative wound infections. Lister's observations were published in 1867 in a treatise entitled *On the Antiseptic Principle in the Practice of Surgery* (12). In the following excerpt from this treatise, Lister identifies the chemical agent that he used.

> "The material which I have employed is carbolic acid, a volatile compound which appears to exercise a peculiarly destructive influence upon low forms of life, and hence is the most powerful antiseptic with which we are at present acquainted."

As indicated, the first antiseptic agent was an acid (carbolic acid, also known as phenol), so Joseph Lister not only discovered antisepsis, he also discovered the antimicrobial value of acidity. Unfortunately, Joseph Lister's contributions are largely forgotten, and the name Lister is recognized mainly in relation to a popular mouthwash, Listerine®!

Antimicrobial Effects

The influence of gastric pH on the growth of a pathogenic organism is shown in Figure 4.3 (13). The pathogen in this case is *Salmonella typhimurium*, a common cause of infectious enteritis in humans. The graph in Figure 4.3 shows the growth pattern of *S. typhimurium* in gastric

secretions at three different pH levels. Note that the organism thrives at a pH of 4, but there is a steady decline in survival at a pH of 3, and the organism is completely eradicated after one hour at a pH of 2. The pH of gastric secretions is 1–2, so gastric acidity should be very effective in eradicating ingested pathogens.

The role of gastric acidity as an antimicrobial defense mechanism is demonstrated by the consequences of gastric acid suppression (by histamine H_2 receptor antagonists or proton pump inhibitors), which includes an increased risk of infectious gastroenteritis from *Salmonella* and *Campylobacter* species (11,14–16), and an increased incidence of *Clostridium difficile* infections (17). (This topic will resurface later in the chapter.)

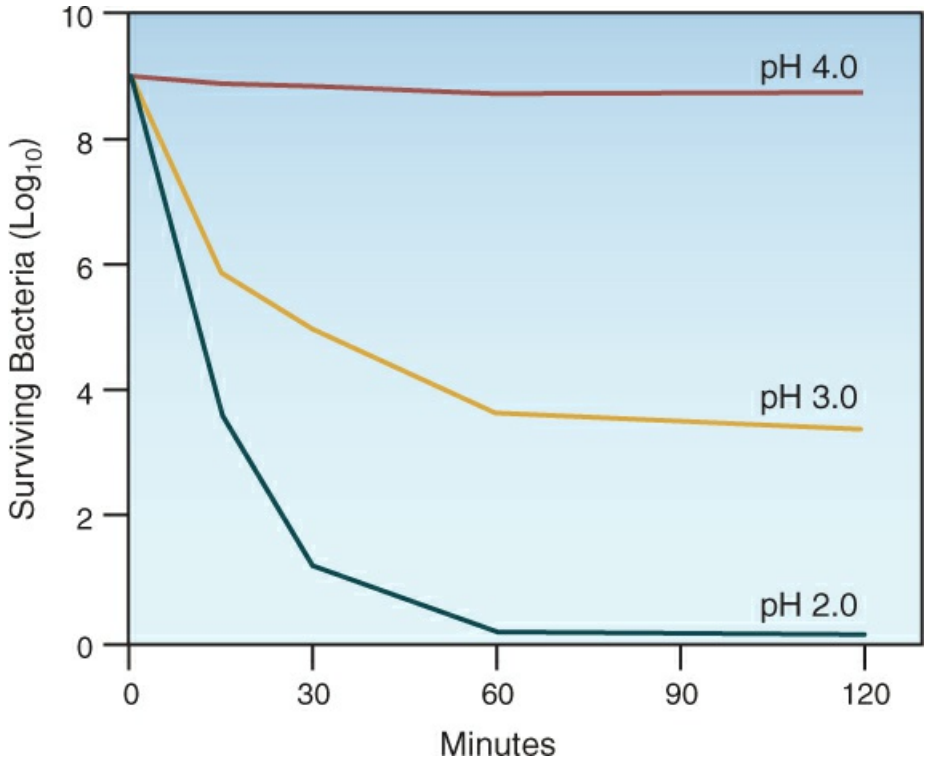

FIGURE 4.3 The influence of gastric pH on the growth of *Salmonella typhimurium*, a common cause of infectious enteritis. (From Reference 13).

ALIMENTARY DECONTAMINATION

Patients who are seriously ill are prone to colonization of the oropharynx and GI tract with pathogenic organisms, and the following decontamination methods are used to limit this process.

Oral Decontamination

The aspiration of mouth secretions into the upper airways is believed to be the inciting event in most cases of hospital-acquired pneumonia (18). The volume of saliva produced daily averages about 750 mL in adults, and each mL of saliva contains about one million microorganisms (see Figure 4.1). Therefore, aspiration of 0.13% (1/750) of the daily saliva volume will introduce a million microbes into the airways. This not a concern in healthy subjects, because the

oropharynx is colonized with organisms that show little proclivity for harm. Not so in critically ill patients, as described next.

Colonization of the Oropharynx

The oropharynx of seriously ill patients becomes colonized with pathogenic organisms, most notably aerobic gram negative bacilli like *Pseudomonas aeruginosa* (18,19). This colonization is not environmentally driven, but is directly related to the presence and severity of illness. This is demonstrated in Figure 4.4 (19), which shows that healthy subjects are not colonized with aerobic gram-negative bacilli, regardless of the environment.

Pathogenic colonization of the oropharynx is caused by a change in bacterial adherence to the surface epithelium. Epithelial cells have specialized adhesion proteins that bind specific groups or species of bacteria, and in the presence of a serious illness, there is a conformational change in these proteins that results in the ability to bind pathogens. This same process occurs in the bowel mucosa and the bladder epithelium, and it demonstrates that *the determining factor in the colonization of epithelial surfaces is not the presence of an organism, but the ability of the organism to bind to the epithelium*. This topic deserves much more attention, as the prevention of pathogen binding to epithelial surfaces would be an effective method of infection control.

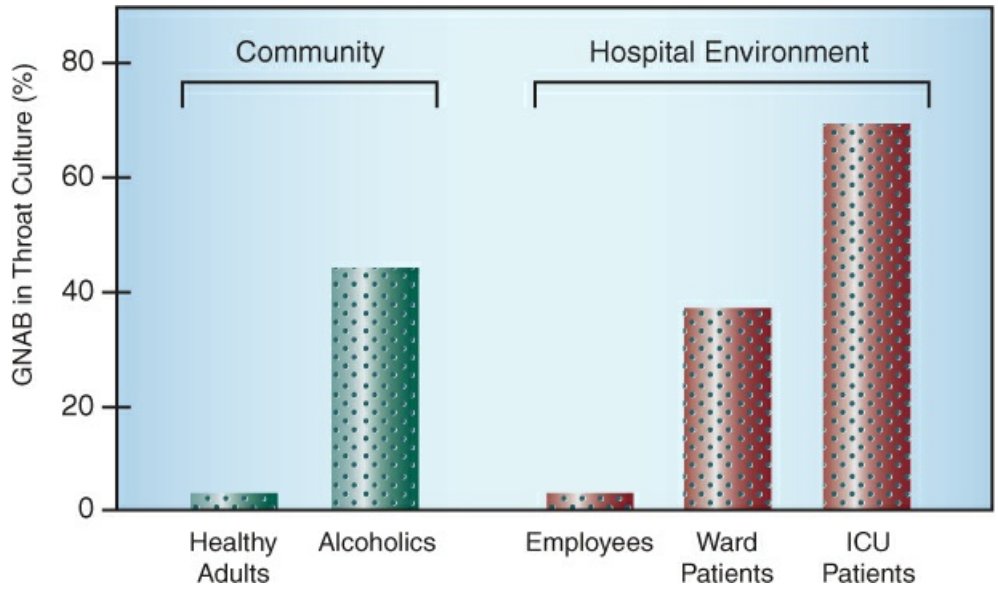

FIGURE 4.4 The prevalence of Gram negative aerobic bacilli (*GNAB*) in cultures of the oral cavity in selected groups of subjects. (From Reference 19).

TABLE 4.1 Oral Decontamination Methods

Method	Regimen
Chlorhexidine	• Apply a 0.12% chlorhexidine gluconate solution to the oral mucosa every 6 hours. • Avoid the 2% chlorhexidine solution, which can cause an ulcerating mucositis.
Selective Oral Decontamination†	• Have pharmacy prepare a gel mixture of 2% gentamicin, 2% colistin, and 2% vancomycin. • Apply this gel to the oral mucosa with a gloved finger every 6 hours.

†Regimen from Reference 27.

Colonization of the oropharynx with gram-negative bacilli is a prelude to pneumonia, since the same organisms (gram-negative bacilli) are the most frequent cause of nosocomial pneumonias (see Chapter 29). This is the rationale for oral decontamination, which is currently reserved for patients who are intubated and receiving mechanical ventilation. There are two methods of oral decontamination: one uses an antiseptic oral rinse, and the other involves the local application of nonabsorbable antibiotics. Both methods are summarized in Table 4.1.

Chlorhexidine

The popular skin antiseptic chlorhexidine has been adopted for use in decontaminating the oropharynx. A 0.12% solution of chlorhexidine gluconate is used as an oral rinse every 6 hours, and this regimen continues for as long as the patient is ventilator-dependent. There is a more concentrated (2%) chlorhexidine gluconate solution, but this is less desirable because it can cause a mucositis (20).

The benefit of oral decontamination with chlorhexidine has been difficult to establish. Some studies have shown a 30% relative reduction in the incidence of ventilator-associated pneumonia, without an associated decrease in mortality (21). However, other studies have shown marginal or no benefit (22), and the pooled results of 11 clinical trials has shown an increase in mortality associated with chlorhexidine (23). Because of concerns about the potential for harm, the international guidelines on ventilator-associated pneumonia withdrew a recommendation for oral decontamination with chlorhexidine (24), and experts in the United States have followed suit (25). Unfortunately, there is no other antiseptic agent that has been adequately studied for oral decontamination.

An additional problem with chlorhexidine that is rarely mentioned is its limited spectrum of activity; i.e. *chlorhexidine is effective primarily against gram-positive organisms (26), while gram-negative organisms are the predominant microbes in the oropharynx of critically ill patients*. This would explain the disappointing results of the clinical trials just mentioned.

Selective Oral Decontamination

The principle behind selective oral decontamination (SOD) is to eradicate colonization with pathogens while preserving the normal microbial population of the oropharynx. This is achieved with a combination of nonabsorbable antibiotics that are locally applied to the oral mucosa. One SOD regimen that has had success in reducing the risk of ventilator-associated pneumonia is shown in Table 4.1 (27). In this case, a mixture of 2% gentamicin, 2% colistin, and 2% vancomycin is applied as a paste to the oral mucosa four times daily. This regimen is designed to eradicate staphylococci, gram-negative aerobic bacilli, and *Candida* species, but has little activity against anaerobic organisms (normal mouth flora).

EFFICACY: Several clinical studies have shown that SOD reduces the incidence of ventilator-associated pneumonia (23,28,29), and also reduces the frequency of bacteremias involving gram-negative bacilli (29,30). This latter observation is demonstrated in Figure 4.5 (29). Both graphs in this figure show a 33% (relative) decrease in the incidence of gram-negative bacteremias associated with SOD.

Despite convincing evidence that SOD is effective in reducing the frequency of ICU-acquired infections, SOD is largely ignored. On the other hand, despite evidence of limited efficacy and possible harm, chlorhexidine has been the standard method of oral decontamination. This scenario is the antithesis of evidence-based medicine! The rationale for ignoring SOD is the fear of antibiotic resistance; an unfounded fear that is addressed at the end of the next section.

Selective Digestive Decontamination

Selective digestive decontamination (SDD) is based on the same principle as SOD (i.e., prevent colonization with pathogens while preserving the normal microflora), but is applied to the entire alimentary tract. An SDD regimen that has proven successful is shown below (30).

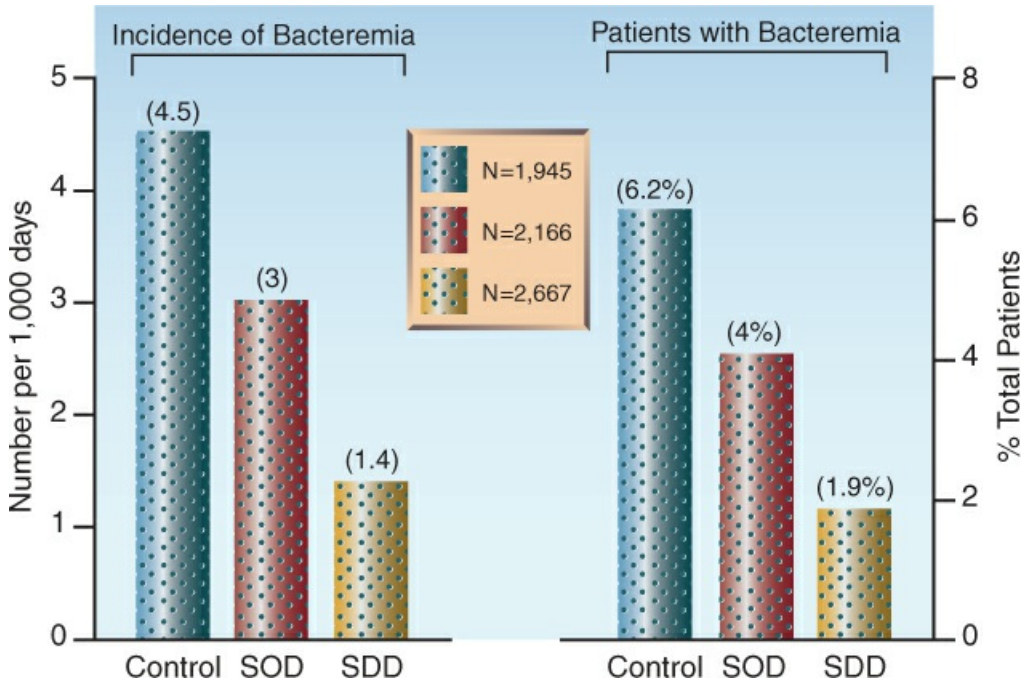

FIGURE 4.5 The prevalence of gram-negative bacteremia in patients randomized to receive selective oral decontamination (SOD), selective digestive decontamination (SDD), or standard care (control). The graph on the left shows the number of bacteremias per 1000 days, and the graph on the right shows the percentage of patients with bacteremia. *N* is the number of patients in each study group. (From Reference 29).

Mouth: A gel containing 2% polymyxin, 2% tobramycin, and 2% amphotericin is applied to the oral mucosa every 6 hours.

GI tract: A 10 mL aliquot of a solution containing 100 mg polymyxin E, 80 mg tobramycin, and 500 mg amphotericin is delivered through a nasogastric tube every 6 hours.

Systemic: Intravenous cefuroxime, 1.5 grams every 8 hours, is used for the first four days.

This nonabsorbable antibiotic combination is designed to eradicate staphylococci, gram-negative aerobic bacilli, and *Candida* species, while sparing the normal microflora of the

oropharynx and GI tract (mainly anaerobes) The intravenous antibiotic is used for systemic protection until decontamination of the bowel is completed, which takes about 5–7 days. The SDD regimen is intended for all patients who will stay in the ICU longer than 72 hours, and is continued until discharge from the ICU.

Efficacy

Numerous clinical studies have shown that SDD reduces the incidence of ICU-acquired infections (including pneumonias, urinary tract infections, and bacteremias), and also significantly reduces the mortality rate (29–34). The impact of SDD on gram-negative bacteremia is demonstrated in Figure 4.5 (29). Note that SDD was associated with a marked (67%) reduction in the frequency of these infections. This effect is lost for bacteremias involving multidrug-resistance gram-negative bacilli (35), indicating that SDD is not appropriate in ICUs with problematic antibiotic resistance.

SOMETHING OF INTEREST: One observation that deserves mention comes from a clinical study where SDD *eliminated* vascular catheter-related bacteremias (32). This suggests that the bowel is the source of catheter-related bacteremias (not the skin); a concept that is presented at the very end of Chapter 3 (see A FINAL WORD).

Why is SDD Ignored?

Despite numerous studies over the past 30 years showing that SDD is an effective method of reducing ICU-acquired infections, SDD is ignored (like SOD). Much of this is the result of the age-old fear that SDD will promote the emergence of antibiotic resistant organisms. However, none of the SDD studies has shown an increase in infections from antibiotic-resistant organisms, including a prospective study evaluating SDD over a 5-year period (36), and a 16-year experience with SDD (37). Thus, the disregard for SDD is not validated by clinical studies.

Probiotics

Probiotics are microbial preparations of normal but harmless inhabitants of the intestinal tract that are capable of preventing colonization with pathogenic organisms. (*Note:* Probiotics should be distinguished from *prebiotics*, which are food substances—mostly dietary fibers—that promote the growth of normal bowel microflora. Probiotics and prebiotics are often combined to create what is known as *synbiotic therapy*.) The most common probiotics are strains of lactic acid bacteria, such as *Lactobacillus* and *Bifidobacterium* species, that are resistant to the bactericidal actions of gastric acid and bile salts, and can successfully colonize the bowel when ingested (38). Another popular probiotic is the *Saccharomyces* fungus, which is the principal ingredient in brewer's yeast and baker's yeast.

Clinical Use

The principal use of probiotics in the ICU is the prevention of *Clostridium difficile* infections during antibiotic therapy (39). This effect is time-limited; the combined results of 19 clinical studies showed that probiotics reduced the risk of *C. difficile* infections only when started within 2 days of antibiotic therapy (40). Probiotic therapy can also reduce the risk of hepatic encephalopathy (41) and ventilator-associated pneumonia (42).

STRESS-RELATED MUCOSAL INJURY

Stress-related mucosal injury is a term used for superficial erosions on the luminal surface of the stomach that are found in critically ill patients. These erosions can be confined to the mucosa, or they can bore deeper into the submucosa. The deeper erosions are called *stress ulcers*, and are more likely to cause troublesome bleeding. Hereafter, both types of surface erosions will be referred to as stress ulcers.

Pathogenesis

The surface epithelial cells in the stomach are covered with a layer of bicarbonate-rich mucus (pH = 7) that protects the cells from the acidity of gastric secretions, and from proteolytic enzymes (e.g., pepsin) in the secretions. Gastric mucosal blood flow plays an important role in preserving the mucous layer by providing nutrients to support the functional integrity of the surface epithelial cells. The importance of mucosal blood flow is demonstrated by the fact that 70–90% of the blood supply to the stomach is delivered to the gastric mucosa (43). The endothelial cells in surface vessels secrete prostacyclin and nitric oxide, which are both instrumental in maintaining nutrient flow to the gastric mucosa (44).

Local ischemia is the inciting event in stress-related mucosal injury, while the presence of luminal acid is believed to aggravate the condition (44). In animal models of hemorrhagic shock, reperfusion injury also plays a role (45). Of interest, occult gastric hypoperfusion can be a frequent occurrence in critically ill patients who are not hypotensive, especially in those receiving mechanical ventilation (44).

Stress Ulcer Bleeding

Erosions are visible on the surface of the stomach in 75% to 100% of patients within 24 hours of admission to the ICU (46). These lesions often ooze blood from eroding into superficial capillaries, but “clinically significant” bleeding is infrequent. The accepted definition of clinically significant bleeding is overt bleeding that is accompanied by at least one of the following: (a) a decrease in blood pressure (systolic, mean, or diastolic pressure) of ≥20 mm Hg, (b) initiation of vasopressor therapy, or a 20% increase in the vasopressor dose, (c) a decrease in hemoglobin of at least 2 g/dL, or (d) transfusion of 2 or more units of packed red blood cells (47,48). The likelihood of significant stress ulcer bleeding is determined by the presence or absence of specific risk factors, as described next.

Risk of Bleeding

The risk of significant bleeding from stress ulcers can be stratified as shown in Table 4.2, which is taken from the most recent clinical practice guidelines on the prevention of stress ulcer bleeding (47). The following points in this table deserve emphasis:

. The risk of bleeding during mechanical ventilation is decreased considerably by enteral tube feedings.

. Corticosteroid therapy is not a significant risk factor for stress ulcer bleeding, and does not require prophylactic therapy. Ditto for therapeutic anticoagulation.

THE STEROID MYTHOS: The popular perception that corticosteroid therapy creates a significant risk of stress ulcer bleeding (and warrants prophylactic therapy) has a surprising lack of experimental support. The most recent evaluation of this issue is a report of the pooled results from 25 studies (49), which showed that corticosteroid therapy had no influence on GI bleeding of any severity. Results like this indicate that corticosteroid therapy should not be considered a risk factor for stress ulcer bleeding.

TABLE 4.2 Identifying the Risk of Significant Stress Ulcer Bleeding

Risk Level[1]	Prophylaxis?	Conditions
Highest Risk (8–10%)	Yes	1. Mechanical ventilation >24 hrs without enteral feedings 2. Chronic liver disease[2]
High Risk (4–8%) (cutoff for prophylaxis)	Yes	1. Worrisome coagulopathy[3] 2. At least 2 conditions from the moderate risk level
Moderate Risk (2–4%)	No	1. Mechanical ventilation >24 hrs with enteral feedings 2. Acute kidney injury 3. Sepsis 4. Shock
Low Risk (1–2%)	No	1. Acute liver failure 2. Anticoagulant therapy 3. Steroid therapy 4. Immunosuppressive therapy 5. Cancer 6. No risk factors

From the clinical practice guideline in Reference 47. See text for definition of significant bleeding.

[1]Numbers in parentheses indicate % patients with significant bleeding.

[2]Cirrhosis with portal hypertension.

[3]Platelets <50 x 10^9/L, INR >1.5, or prothrombin time >20 seconds.

Prophylaxis for Stress Ulcer Bleeding

Surveys indicate that a majority (>80%) of ICU patients receive prophylactic therapy for stress ulcer bleeding, and about 70% of these patients do not need prophylaxis (50). This excessive use of stress ulcer prophylaxis is not only costly, it can also be harmful (see later).

The principal method of prophylaxis for stress ulcer bleeding is the suppression of gastric acid production with proton pump inhibitors (PPIs) or histamine type-2 receptor antagonists (H_2 blockers). (The goal is to maintain a pH ≥4 in gastric aspirates, although this is rarely monitored.) The other, less popular, method employs a cytoprotective agent (sucralfate) that forms a protective covering over damaged areas of the gastric mucosa, and does not alter gastric acidity. The individual drugs and recommended doses are shown in Table 4.3.

TABLE 4.3 Drugs Used for Prophylaxis of Stress Ulcer Bleeding

Drug	Type	Routes	Dosage
Famotidine	H_2 Blocker	PO, NG, IV	20 mg every 12 hrs†
Pantoprazole	PPI	PO, NG, IV	40 mg once daily
Omeprazole	PPI	PO, NG	40 mg once daily
Lansoprazole	PPI	PO, NG	30 mg once daily
Sucralfate	Protectant	PO, NG	1 g every 6 hrs

†A dose reduction of 50% is recommended for a creatinine clearance <50 mL/min.
PPI = proton pump inhibitor.

Efficacy

All three types of drugs (PPIs, H_2 blockers, and sucralfate) are capable of reducing the risk of stress ulcer bleeding (51). The relative efficacy is: PPIs >H_2 blockers > sucralfate (51–53). However, none of these agents provides a survival benefit (51–53).

H_2 Blockers

Histamine H_2 receptor antagonists, or H_2 blockers, (cimetidine, famotidine) inhibit gastric acid secretion by binding to histamine H_2 receptors on gastric parietal cells. Famotidine is currently the favored H_2 blocker for stress ulcer prophylaxis, and is well suited for ICU patients because it can be given intravenously. The H_2 blockers are cleared by the kidneys, and reduced drug clearance from renal insufficiency can have neurotoxic effects (e.g., altered mentation). For this reason, a 50% reduction in the daily dose is advised for patients with a creatinine clearance <50 mL/min (54).

Proton Pump Inhibitors (PPIs)

The PPIs (omeprazole, esomeprazole, pantoprazole, lansoprazole), are potent acid-suppressing drugs that block the secretion of hydrogen ions by gastric parietal cells. These drugs are actually prodrugs, and are converted to the active form within gastric parietal cells. Once activated, the drugs bind irreversibly to the membrane pump responsible for hydrogen ion secretion, and this results in complete inhibition of gastric acid secretion.

All PPIs are considered equivalent as prophylactic agents (although this has not been studied), but pantoprazole is the most popular PPI in ICU patients because it can be given intravenously (48). (*Note:* Esomeprazole can also be given intravenously, but this drug is rarely used for stress ulcer prophylaxis.) Unlike H_2 blockers, PPIs require no dose adjustment for renal insufficiency.

The graph on the left in Figure 4.6 shows the effect of pantoprazole (40 mg IV once daily) on (significant) stress ulcer bleeding in more than 3,000 high-risk ICU patients (48). Note the low incidence of GI bleeding in the control patients (4.2%), and the small (1.7%) treatment effect. Small benefits like this must be measured against the risks associated with gastric acid suppression (see later).

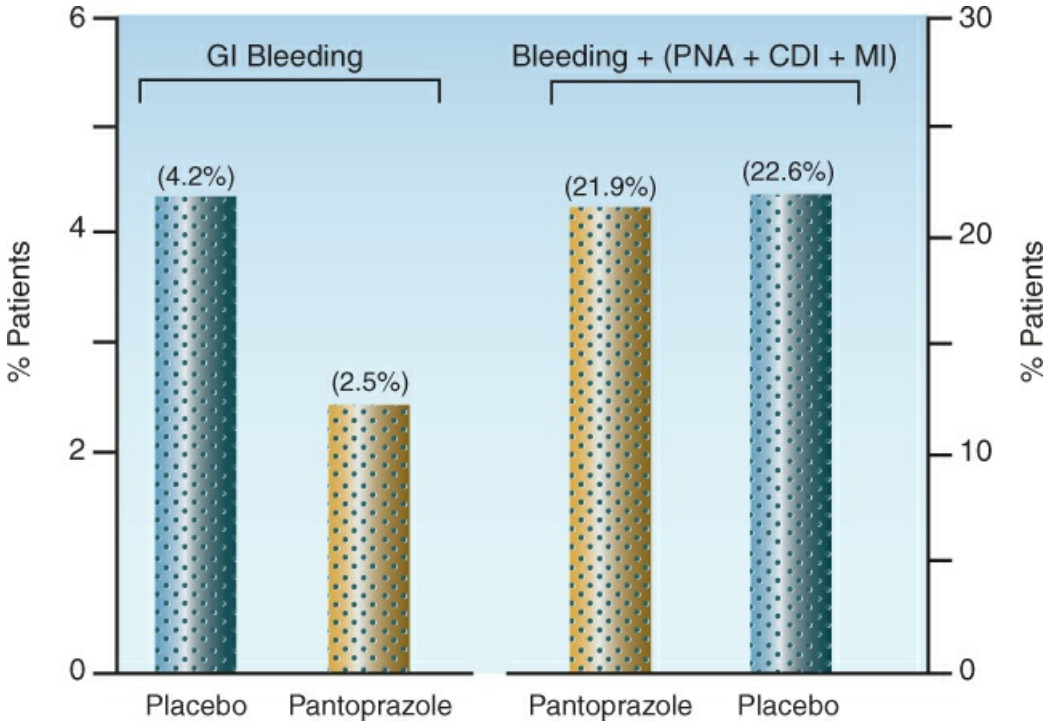

FIGURE 4.6 Effects of stress ulcer prophylaxis with pantoprazole (40 mg IV daily) on the incidence of significant GI bleeding (graph on the left) and the summed incidence of GI bleeding and the risks associated with pantoprazole: pneumonia (PNA), *C. difficile* infection (CDI), and myocardial ischemia (MI)) which is shown in the graph on the right. Data from a study of 3,298 high-risk ICU patients from 6 different countries (48). See text for further explanation.

PPIs AND CLOPIDOGREL: PPIs interact with clopidogrel, an antiplatelet agent that has been used for secondary prevention of acute coronary syndromes and stroke. Clopidogrel is a prodrug that is converted to its active form by the same (cytochrome P-450) pathway in the liver that metabolizes PPIs. As a result, PPIs can impede clopidogrel activation in the liver (by competitive inhibition) and reduce its antiplatelet effect (55). This interaction has been implicated as a risk factor for the recurrence of acute coronary syndromes following percutaneous coronary intervention (56), but evidence of a causal link has been inconsistent. At the present time, there is no recommendation to avoid PPIs in patients receiving clopidogrel.

Risks of Gastric Acid Suppression

The risk of gastric acid suppression is related to loss of the antimicrobial activity of gastric acidity. The major risks are summarized below.

***Clostridium Difficile* INFECTION:** The association between gastric acid suppression and *Clostridium difficile* infections has been reported in outpatients (57), inpatients (58), and ICU patients (59,60), and the association is stronger with PPIs than with H_2 blockers (57,61). Patients who receive PPIs for stress ulcer prophylaxis are three times more likely to develop *C. difficile* enterocolitis (60). In recognition of this risk, The U.S. Food and Drug Administration issued a Drug Safety Alert in 2013 that highlighted the risk of *C. difficile* infections associated with PPIs (62).

PNEUMONIA: There is also an association between gastric acid suppression and an increased risk of pneumonia, including community-acquired pneumonia (63) and ventilator-associated pneumonia (61). Once again, the risk is greater with PPIs than with H_2 blockers (61). The presumed mechanism is colonization of gastric secretions with pathogenic organisms, and subsequent aspiration of infectious gastric secretions into the upper airways.

Benefits vs. Risks

There is evidence that the benefit of PPIs in reducing stress ulcer bleeding is negated or counterbalanced by the adverse consequences of PPIs. This is demonstrated in Figure 4.6 (48). As mentioned earlier, the graph on the left shows a decrease in the incidence of stress ulcer bleeding associated with a PPI (pantoprazole). The graph on the right shows the composite incidence of stress ulcer bleeding plus the risks associated with PPIs (i.e., *C. difficile* infection, pneumonia, and myocardial ischemia related to the clopidogrel interaction). Note that the total incidence of adverse events is no different in the placebo group and the pantoprazole group. This means that the benefit of pantoprazole prophylaxis is erased if you also consider the adverse consequences of PPI therapy; i.e., there is no net benefit from stress ulcer prophylaxis with PPIs.

Sucralfate

Sucralfate is an aluminum salt of sucrose sulfate that adheres to damaged areas of the gastric mucosa, and forms a viscous covering that shields the denuded surface from luminal acids and pepsin proteolysis. Gastric acidity is maintained, which is the most desirable feature of prophylaxis with sucralfate. At a dose of one gram every 6 hours (usually given as an oral suspension), sucralfate has been shown to reduce the incidence of stress ulcer bleeding (51). Of particular importance, pneumonia is less frequent when sucralfate is used instead of gastric acid-suppressing drugs (64).

Sucralfate has one undesirable feature that precludes its use in a majority of ICU patients: i.e., it can not be used in conjunction with enteral tube feedings. Sucralfate must be given when the stomach is empty (to allow binding to the gastric mucosa), which is not possible during enteral feedings without lengthy interruptions to allow gastric emptying. Even with interruptions, any mixing of sucralfate with tube feedings is problematic because it can promote bezoar formation (65).

Another undesirable feature of sucralfate is the ability to bind certain drugs in the stomach (by virtue of its aluminum moieties), including ciprofloxacin, digoxin, ketoconazole, norfloxacin, phenytoin, thyroxine, tetracycline, theophylline, and warfarin (66). The aluminum in sucralfate can also bind phosphate in the bowel, but this rarely results in hypophosphatemia (67).

The Case Against Stress Ulcer Prophylaxis

The relevant observations about stress ulcer prophylaxis are listed in Table 4.4. These observations indicate that stress ulcer prophylaxis with gastric acid-suppressing drugs provides little or no benefit, and can introduce harm.

The emerging realization that stress ulcer prophylaxis is “more trouble than it’s worth” has prompted efforts to “deprescribe” proton pump inhibitors in high-risk ICU patients. At this time, six clinical trials have shown that withholding pantoprazole in high-risk ICU patients does not increase the occurrence of significant stress ulcer bleeding (68). This differs from earlier studies

showing a decrease in stress ulcer bleeding with PPI prophylaxis, and this difference can be attributed to improvements in enteral nutrition (see next).

Enteral Feeding

Enteral tube feedings can protect against stress ulcer bleeding in two ways. First, enteral feeding has a trophic effect on the gastric mucosa that limits or prevents mucosal breakdown (see Chapter 49). Second, the presence of feeding solutions in the stomach will raise the pH of gastric contents. The prophylactic value of enteral feedings is revealed in the combined results of three clinical studies, which showed that the ability of gastric acid-suppressing drugs to reduce stress ulcer bleeding was lost when patients received a full regimen of enteral tube feedings (69). These results indicate that *enteral feeding is all that is needed for stress ulcer prophylaxis*.

TABLE 4.4 The Case Against Stress Ulcer Prophylaxis

A composite of the following observations indicates that the routine use of stress ulcer prophylaxis (SUP) is not warranted.
• Significant bleeding from stress ulcers is infrequent. • SUP has only a small treatment effect. • There is no survival benefit with SUP. • The benefit of SUP is lost when the risks of gastric acid suppression are considered.

A FINAL WORD

Gastric Acidophobia

One of the recurring themes in this book is the importance of the bowel as a source of ICU-acquired infections, and the risk of these infections is enhanced by the popular (and overly excessive) use of gastric acid suppression for stress ulcer prophylaxis. This practice is rooted in the time-honored fear that acids are corrosive. While acids can corrode certain metals like iron, this does not apply to organic (carbon-based) matter. Consider the following beverages with pH values that are close to gastric acid (70):

Source	pH
Gastric Acid	2.0
Lemon Juice	2.0
Pepsi	2.13
Vinegar	2.2
Coca-Cola	2.24
Fanta	2.51

Despite levels of acidity that are comparable to gastric acid, these beverages are not harmful.

(Imagine what would happen if Pepsi or Coca-Cola caused mouth burns!) In fact, vinegar is used to *preserve* organic matter (foods); a process known as *pickling*. When an industrial acid causes skin burns, the culprit is the chemical composition of the acid, not the acidity.

We are designed to have acid in our stomach, to protect the intestinal microbiome from foreign invaders, and endowing this acid with the ability to cause harm is contrary to the survival of our species. The cause of stress-related mucosal injury is hypoperfusion of the gastric mucosa, not the acidity of gastric secretions.

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Chapter 5

Venous Thromboprophylaxis

Two words best characterize the mortality and morbidity due to venous thromboembolism in the United States: substantial and unacceptable.

Kenneth M. Moser, MD (*a*)

To supplement Dr. Moser's statement, venous thromboembolism (i.e., deep venous thrombosis and pulmonary embolism) has four "alliterative" attributes: i.e., it is common, often covert, can be catastrophic, but is correctable. The risk of venous thromboembolism is almost universal in the patients who inhabit medical and surgical ICUs. Thrombus formation is most prominent in the major veins that drain the lower extremities (i.e., the femoral and iliac veins), and it often remains clinically silent until a portion (or all) of the thrombus breaks free and travels to the lungs to become a pulmonary embolus, which can be a life-threatening and even fatal event. Fortunately, there are a variety of preventive measures that can reduce or eliminate the risk of this life-endangering process.

Venous thromboembolism has been cited as the leading cause of preventable deaths in hospitalized patients, and preventive measures thus become "the number one priority for improving patient safety in hospitals" (1). This chapter addresses this mandate by describing the various methods used to prevent venous thromboembolism (i.e., *venous thromboprophylaxis*), and which methods work best in different clinical situations. Many of the recommendations in this chapter are taken from the clinical practice guidelines and reviews listed at the end of the chapter (2–11). (*Note:* The diagnosis and treatment of venous thromboembolism are described in Chapter 22.)

RISK FACTORS

There are a wide variety of risk factors for venous thromboembolism (VTE) in hospitalized patients, and these are organized in Table 5.1. The expression of these risk factors in different groups of patients is shown in Figure 5.1 (9).

Major Surgery

Major surgery (i.e., surgery performed under general or spinal anesthesia that lasts longer than 45 minutes) is the most recognized cause of VTE in hospitalized patients, and is responsible for about one-third of deaths from VTE (4). All major surgical procedures create a heightened risk of VTE, which can persist for 6–12 weeks (i.e., after hospital discharge) (11). The risk is particularly high with cancer-related surgery (2,4,10), bariatric surgery (3), and orthopedic procedures involving the hip and knee (2,5).

The risk of VTE after major surgery is attributed to several factors, including thromboplastin release during the procedure (which produces a hypercoagulable state that lasts for days), inflammation (from prolonged procedures), vascular injury (especially in orthopedic and peripheral vascular procedures) and extended periods of bed rest in the perioperative period.

TABLE 5.1 Risk Factors for Venous Thromboembolism

Categories	Conditions
Surgery	Major surgery, especially hip and knee replacement, cancer-related surgery, and bariatric surgery.
Trauma	Traumatic brain injury, fractures of the spine, pelvis, hip, or lower extremities, extensive tissue and burn injuries.
Malignancy	Solid tumors (especially pancreatic and gastric CA), hematologic malignancies, chemotherapy.
Acute medical Illness	Acute stroke with lower extremity weakness, heart failure with leg edema, COVID-19, sepsis, limited mobility.
ICU-Related	Mechanical ventilation, neuromuscular paralysis, central venous catheters, circulatory shock, vasopressors, platelet transfusions, prolonged immobility.
Patient-Specific	Prior VTE, family history of VTE, genetic risk factors, age >70, obesity, pregnancy or postpartum.

Major Trauma

The risk of VTE is highest following major or multisystem trauma, where the reported incidence of DVT is 58% without prophylaxis (6). The trauma conditions with the highest risk of VTE are brain and spinal cord injuries, spinal fractures, and fractures of the pelvis, hip, and long bones of the legs. There are several factors that predispose to VTE in trauma, including thromboplastin release and inflammation from extensive tissue injury, vascular injury, long bone fractures (which release thrombogenic lipids into the circulation), and prolonged periods of immobility from lower extremity injuries.

Acute Medical Illness

Hospitalization for acute medical illness is associated with an eightfold increase in the risk of VTE (8). Although VTE is less common in medical patients than in surgical patients or trauma victims (see Figure 5.1), medical patients account for a majority (50% to 75%) of VTE events in hospitalized patients (8). The conditions that create the highest risk of VTE are neoplastic diseases, acute stroke with weakness of the extremities, and right-sided heart failure with leg edema. (*Note:* COVID-19 is associated with a high risk of VTE, but this illness seems to have

subsided.)

ICU Patients

As mentioned earlier, a majority of ICU patients have one or more of the risk factors for VTE listed in Table 5.1. There are also ICU-specific factors that add further to the risk of VTE, which include prolonged mechanical ventilation (>48 hrs.), systemic inflammatory conditions (e.g., sepsis), circulatory shock, vasopressor infusions, platelet transfusions, and the presence of central venous catheters or peripherally inserted central catheters (PICCs).

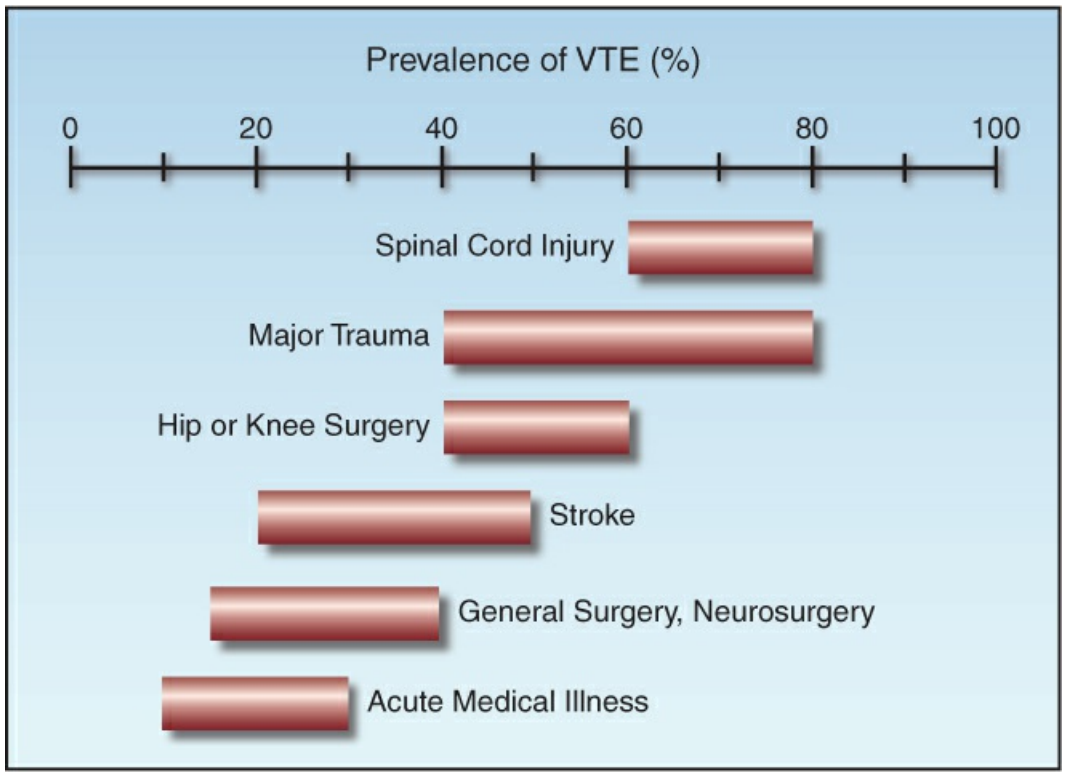

FIGURE 5.1 Risk of venous thromboembolism (VTE) without thromboprophylaxis, in different groups of patients. Includes both symptomatic and asymptomatic cases. From Reference 9.

Patient-Specific Factors

Patient–specific risk factors for VTE include advanced age, obesity, pregnancy, personal or family history of VTE, and genetic predisposition to thrombosis (e.g., Factor V deficiency, antithrombin III deficiency). The factors that confer the highest risk of VTE include a prior history of VTE, and the genetic risk factors; e.g., inherited antithrombin III deficiency creates a 14-fold increase in the risk of VTE (11).

PARENTERAL PROPHYLACTIC REGIMENS

A number of anticoagulant regimens have proven effective in reducing the incidence of VTE in hospitalized patients (2–8), but the following considerations are needed before starting an

anticoagulant regimen:

. Absolute contraindications include intracranial hemorrhage and "clinically important" bleeding, which is defined as blood loss associated with a decrease in systolic blood pressure ≥20 mm Hg, a decrease in hemoglobin ≥2 g/dL, or the need to transfuse at least 2 units of packed red blood cells.

. Relative contraindications include traumatic head and spinal injury, a history of recurrent GI bleeding, and a severe coagulopathy (e.g., platelets <50,000).

. Menstrual bleeding is not a contraindication to anticoagulant prophylaxis.

Anticoagulant prophylaxis is typically achieved by subcutaneous injection, using the drug regimens summarized in Table 5.2.

TABLE 5.2 Thromboprophylaxis with Parenteral Agents

Agent	Prophylactic Dosing Regimen
Unfractionated Heparin	Standard: 5,000 Units SC every 8–12 hrs. Obesity: 7,500 units every 8 hrs for BMI ≥ 40 kg/m^2. Renal: No dose adjustment.
Enoxaparin (Lovenox)	Standard: 40 mg SC once daily, or 30 mg SC every 12 hrs. Obesity: 40 mg SC every 12 hrs for BMI ≥ 40 kg/m^2. Renal: If Cr CL < 30 mL/min, reduce dose to 30 mg SC once daily, or use UFH.
Dalteparin (Fragmin)	Standard: 2,500–5,000 units SC once daily. Obesity: Not adequately studied. Renal: No dose adjustment.
Fondaparinux (Arixtra)	Standard: 2.5 mg SC once daily. Obesity: No recommendations. Renal: If Cr CL = 35–50 mL/min, reduce dose to 1.5 mg SC once daily. Do not use if Cr CL < 30 mL/min.

From References 14, 15, 17–20, 24, 25. SC = subcutaneous, Cr CL = creatinine clearance, UFH = unfractionated heparin.

Unfractionated Heparin (UFH)

Heparin is a naturally occurring mucopolysaccharide that is made by mast cells in a wide variety of species, including humans. (Porcine intestines and bovine lungs have been the traditional sources of heparin.) Native or "unfractionated" heparin (UFH) is a heterogeneous collection of molecules that vary in size (molecular weight) from 3,000 to 30,000 Daltons (12), and this size variation has an important influence on anticoagulation produced by heparin, as described next.

Mechanisms

Heparin exerts its anticoagulant effect in two ways. First, it binds to antithrombin III (AT) in circulating blood, and this activates the AT and leads to inhibition of activated factor X (Xa), as shown in Figure 5.2. Since factor Xa normally converts prothrombin to thrombin, the inhibition

of factor Xa ("anti-Xa" effect) inhibits the generation of thrombin. In addition to this action, the heparin molecule forms electrostatic bonds with thrombin, and this inhibits the ability of thrombin (factor IIa) to convert fibrinogen to fibrin. This "anti-IIa" effect is size-dependent (i.e., dependent on the length of the polysaccharide chain in the heparin molecule), and this explains why the size variation in UFH preparations produces a variable anticoagulant effect. Overall, the anti-IIa effect is 10 times greater than the anti-Xa effect (13), which is a testament to heparin's ability to form electrostatic bonds with other molecules.

Heparin's tendency for electrostatic binding extends to plasma proteins, endothelial cells, and macrophages. Heparin binding to plasma proteins reduces bioavailability, while heparin binding to endothelial cells and macrophages promotes clearance from the bloodstream. Variations in plasma protein levels add further to the variable anticoagulant effects of heparin.

PLATELET BINDING: Heparin binds to a protein (platelet factor 4) on platelets to form an antigenic complex that can trigger the formation of IgG antibodies. These antibodies can bind to platelets and trigger a platelet activation response, which leads to thrombosis and a consumptive thrombocytopenia. This *heparin-induced thrombocytopenia* is not a dose-dependent phenomenon, and can occur with the low doses of heparin used for thromboprophylaxis. (This condition is described in Chapter 13.)

Prophylactic Dosing

The activation of AT by heparin is a highly sensitive reaction, which means that low doses of heparin can inhibit thrombogenesis. *The dose of unfractionated heparin used for thromboprophylaxis is 5,000 units injected subcutaneously every 8–12 hours.* The 8-hour dosing schedule is popular for higher-risk situations, but most studies show no difference in efficacy (or risk of bleeding) with either regimen (14).

OBESITY: Standard doses of heparin are considered suboptimal in patients with obesity (body mass index or BMI ≥ 30 kg/m^2) because of the increased volume of drug distribution in obesity. As a result, higher doses of heparin have been recommended in obese patients, especially those with morbid obesity (BMI ≥ 40 kg/m^2). A popular regimen for patients with morbid obesity is 7,500 units every 8 hours, which has proven to be more effective in preventing VTE than the standard low-dose regimen (15).

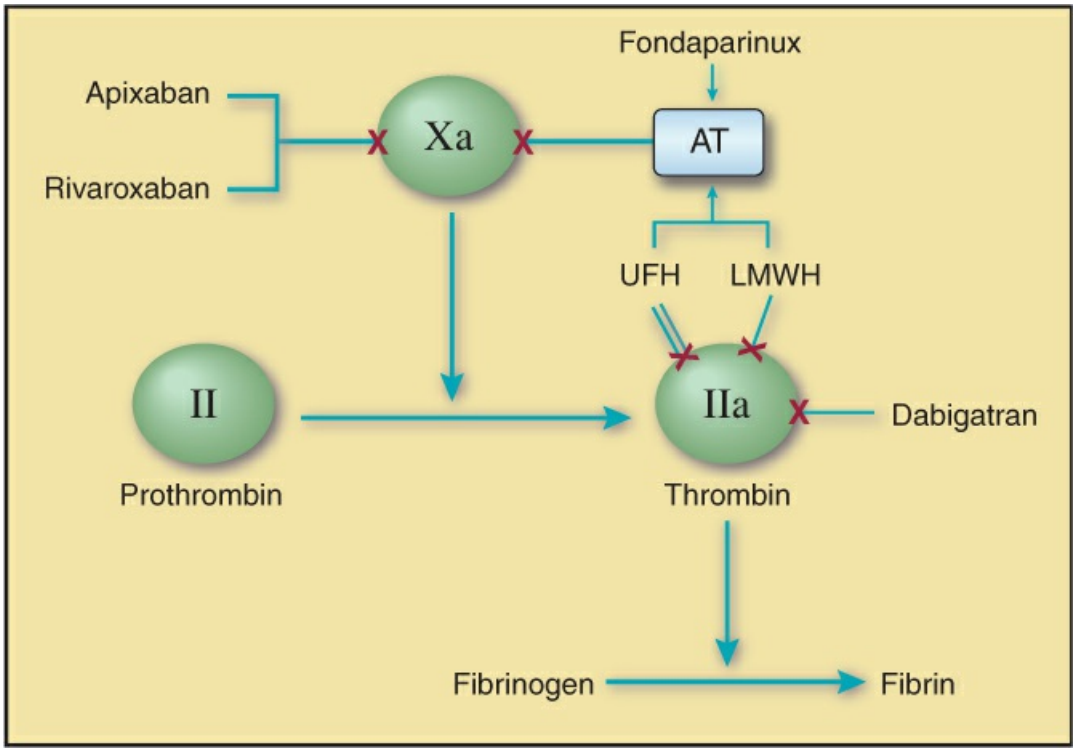

FIGURE 5.2 Mechanisms of anticoagulation with unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) and the direct oral anticoagulants (DOACs). "X" denotes inhibition. See text for further explanation.

Low-Molecular-Weight Heparin (LMWH)

Low-molecular-weight heparin (LMWH) is produced by enzymatic cleavage of heparin molecules, which produces smaller molecules of more uniform size. (The average molecular weight of LMWH is 4,500 Daltons.) Like UFH, the LMWH molecules bind to AT and inhibit factor Xa (anti-Xa effect), but the shorter length of the molecules results in less binding to thrombin and reduces the anti-IIa effect (see Figure 5.2). This reduces the variability of anticoagulation seen with UFH, and gives LMWH a more predictable dose-response profile. This predictability is why laboratory measures of anticoagulation are not monitored during therapy with LMWH.

Other Advantages

LMWH does not bind as readily to plasma proteins, endothelial cells, macrophages, and platelets as UFH, and this gives LMWH the following advantages (13):

. As a result of reduced binding to plasma proteins, the bioavailability of LMWH is greater than that of UFH (90% vs 15–30%, respectively), which means that LMWH is a more potent anticoagulant than UFH (at equivalent doses).

. Reduced binding to endothelial cells and macrophages gives LMWH a longer duration of action than UFH, and this translates to less frequent dosing with LMWH.

. Reduced platelet binding by LMWH results in a lower risk of heparin-induced thrombocytopenia; i.e., the reported incidence of this complication is 0.2% with LMWH,

versus 2.6% with UFH (a ten-fold difference) (16).

In summary, *the advantages of LMWH over UFH include a more predictable and more potent anticoagulant response, less frequent dosing, and less risk of heparin-induced thrombocytopenia*.

Prophylactic Regimens

There are two LMWH preparations available for use in the United States: enoxaparin (Lovenox) and dalteparin (Fragmin), and Table 5.3 shows the prophylactic dosing regimens for each of these agents.

ENOXAPARIN: Enoxaparin was the first LMWH approved for use in the United States (in 1993), and numerous clinical studies have shown it to be both safe and effective for thromboprophylaxis. *The standard dose for thromboprophylaxis is 40 mg given by subcutaneous injection once daily, or 30 mg given twice daily for higher-risk patients*. The following dose adjustments deserve mention:

. Enoxaparin is cleared by the kidneys, and for patients with severe renal impairment (i.e., estimated creatinine clearance, or Cr CL, <30 mL/min), the standard prophylactic dose should be reduced to 30 mg once daily, or an alternative anticoagulant (e.g., UFH) should be used (17,18). The latter option seems to be the best choice when the Cr CL falls below 20 mL/min.

. For morbid obesity (BMI ≥ 40 kg/m^2) a dose of 40 mg every 12 hours has proven superior to standard prophylactic dosing (15). (See later for dosing adjustments related to bariatric surgery.)

Enoxaparin has proven to be both safe and effective for preventing VTE in all high-risk clinical settings (17), and it is more effective than UFH for orthopedic procedures involving the hip and knee (5), and in major trauma (6). It is currently the most popular agent for the prevention of VTE in hospitalized patients. (See later for recommendations in specific clinical settings.)

DALTEPARIN: The other LMWH, dalteparin, does not enjoy the popularity of enoxaparin, even though clinical studies have shown no difference in efficacy between dalteparin and enoxaparin for the prevention of VTE (18). *The prophylactic dose of dalteparin is 2,500–5,000 units given subcutaneously once daily.* Dalteparin has one notable advantage over enoxaparin; i.e., no dose reduction is required in patients with renal failure (19). The appropriate dose of dalteparin in obesity has not been adequately studied. One recommendation, based on an author's clinical experience, is a dose of 200 units/kg daily (actual body weight) (20).

Monitoring Anti-Factor Xa Levels

The adequacy of LMWH dosing can be evaluated by measuring the anti-factor Xa level in blood. This measure is not used routinely during LMWH therapy, but it can useful when the adequacy of fixed LMWH dosing is uncertain (e.g., in obesity). The recommended target range for prophylactic dosing is a peak anti-factor Xa level of 0.2–0.5 IU/mL (21).

Fondaparinux

Fondaparinux (also known as "tiny heparin") is a synthetic analog of the pentasaccharide sequence on heparin that binds it to antithrombin III (AT). It is the first selective factor Xa inhibitor approved for clinical use, and has proven effective for thromboprophylaxis in medical patients (22) and in orthopedic procedures involving the hip and knee (23). *The dose of fondaparinux for thromboprophylaxis is 2.5 mg by subcutaneous injection once daily.* Fondaparinux has a half life of 17 hrs (which allows once-daily dosing), and is excreted by the kidneys. In patients with moderate-to-severe renal impairment (Cr CL of 20–50 mL/min), a reduced dose of 1.5 mg daily is recommended (24,25), and the drug should not be used when the Cr CL is <20 mL/min.

When to Use

Fondaparinux is recommended (along with UFH and LMWH) for hospitalized medical patients who require thromboprophylaxis (7), but it is not popular, and has not been studied in critically ill (ICU) patients. Fondaparinux can also be used for prophylaxis in patients with suspected heparin-induced thrombocytopenia (HIT), or a prior history of HIT (26). While it has been used in patients with confirmed HIT, both with and without thrombosis (26), the approved treatment for HIT is argatroban. (For more on HIT, see Chapter 13.)

PROPHYLAXIS WITH ORAL AGENTS

Thromboprophylaxis with oral agents is receiving increased interest as a result of the increase in extended prophylaxis after hospital discharge (see later). Warfarin was the original oral agent used for prophylaxis, but it is no longer favored because of the delayed onset of action (5–7 days), multiple drug interactions, and need for anticoagulation monitoring (with the INR). The newer oral anticoagulants, which include a direct thrombin inhibitor (dabigatran) and three direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban), have a more rapid onset of action (1–4 hours) and do not require routine monitoring of anticoagulation status. (The actions of these oral agents are depicted in Figure 5.2.) These newer agents are collectively known as direct oral anticoagulants, or DOACs. At the present time, *prophylaxis with DOACs is recommended only for hip and knee replacement surgery* (2).

TABLE 5.3 Thromboprophylaxis with Oral Agents

Agent	Prophylactic Dosing Recommendations
Dabigatran (Pradaxa)	Standard: 110 mg initially, then 220 mg once daily. Obesity: Do not use if BMI ≥ 40 kg/m^2 or wt > 120 kg. Renal: Do not use if Cr CL < 30 mL/min.
Apixaban (Eliquis)	Standard: 2.5 mg twice daily. Obesity: Standard dosing for BMI ≥ 40 kg/m^2 or wt > 120 kg. Renal: Do not use if Cr CL < 15 mL/min.
Rivaroxaban (Xarelto)	Standard: 10 mg once daily. Obesity: Standard dosing for BMI ≥ 40 kg/m^2 or wt > 120 kg.

	Renal: Do not use if Cr CL < 15 mL/min.
Warfarin	Standard: 2.5–5 mg once daily; adjust dose to INR of 1.5–2.5. Obesity: No known dose adjustment. Renal: No dose adjustment.

From References 27–29. Cr CL = creatinine clearance, INR = international normalized ratio.

The dosing recommendations for prophylaxis with oral anticoagulants are summarized in Table 5.3, and some pertinent information about these agents is summarized below. (*Note:* Edoxaban is not included here because there is no approved dosage for thromboprophylaxis.)

- DOACs are contraindicated in patients with severe renal impairment (see Table 5.3); in this setting, warfarin is the only oral agent that can be used safely (27,28).
- Standard prophylactic doses of apixaban and rivaroxaban are equally effective in morbidly obese patients (i.e., BMI ≥ 40 kg.m^2 or wt. >120 kg) (29).
- The absorption of DOACs may be adversely affected by gastric bypass surgery, and (until this matter is studied further), these agents should probably not be used for prophylaxis after this procedure (29).
- All DOACs have proven superior to LMWH for thromboprophylaxis in hip and knee replacement surgery (2,27,28), but dabigatran and rivaroxaban have shown higher bleeding rates than LMWH in some studies (28), and apixaban may be the favored DOAC for these procedures (27).
- Rivaroxaban has been approved for thromboprophylaxis in patients with acute medical illness (30), but a meta-analysis of studies comparing DOACs and LMWHs in acutely ill medical patients shows equivalent efficacy but an increased risk of bleeding with DOACs (31).

The popularity of DOACs for venous thromboprophylaxis is very likely to skyrocket in the upcoming years, similar to what has happened with arterial thromboprophylaxis in atrial fibrillation (which is described in Chapter 19).

Aspirin

Although antiplatelet agents are typically not used for venous thromboprophylaxis, the most recent guidelines from the American Society of Hematology includes a conditional recommendation for aspirin as an effective alternative to anticoagulants for hip or knee replacement surgery (2). Although a dose is not specified, most studies involved low-dose aspirin (81 mg daily). This recommendation was based on studies that often included aspirin in conjunction with anticoagulant therapy; e.g., using anticoagulants in the early postoperative period, followed by aspirin for extended prophylaxis after hospital discharge (32). Therefore, the use of aspirin as the sole prophylactic agent after hip or knee arthroplasty seems unwarranted.

Neuraxial Procedures

Anticoagulant prophylaxis can promote hematoma formation from spinal punctures, or from the insertion and removal of intrathecal and epidural catheters, and these hematomas can compress the spinal cord and produce paralysis. To limit the risk of this complication, anticoagulant

prophylaxis should be withheld before performing these procedures. The following are some guidelines for withholding anticoagulant prophylaxis before these procedures:

. For subcutaneous injections of unfractionated heparin, wait at least 12 hours after the last dose, and for once daily dosing of enoxaparin, wait at least 24 hours (9).

. For the DOACS, the recommended time for withholding anticoagulation is dependent on the renal function. With normal or moderately reduced renal function, the wait time is at least 48 hours for dabigatran and rivaroxaban, and at least 24 hours for apixaban (27). Longer wait times are recommended for more severe cases of renal impairment (see Reference 27 for wait times in relation to creatinine clearance).

MECHANICAL THROMBOPROPHYLAXIS

External compression of the lower extremities can be used to promote venous outflow from the legs and reduce the risk of VTE from venous stasis. This method of *mechanical thromboprophylaxis* is typically used as a replacement for anticoagulant regimens in patients who are bleeding or have a high risk of bleeding, but it can also be used as an adjunct to anticoagulant prophylaxis in a high-risk clinical setting (see later). There are two methods of external leg compression: graded compression stockings and intermittent pneumatic compression.

Graded Compression Stockings

Graded compression stockings (GCS), also known as thromboembolism-deterrent or TED stockings, are designed to create 18 mm Hg external pressure at the ankles and 8 mm Hg external pressure in the thigh (33). The resulting 10 mm Hg pressure gradient acts as a driving force for venous outflow from the legs. These stockings have been shown to reduce the incidence of VTE when used alone after major surgery (34). However, they are the least effective method of thromboprophylaxis, and are never used as sole means of preventing VTE in hospitalized patients.

Intermittent Pneumatic Compression

Intermittent pneumatic compression (IPC) has a dual antithrombotic effect because it promotes both venous flow and fibrinolysis (35). IPC devices typically have two or three inflatable bladders that are pressurized in sequence (from distal to proximal). The external leg pressure is about 35–40 mm Hg at the ankle, and 20 mm Hg at the thigh (33), and the compression cycle is typically 10 seconds (6 inflations per minute). (The applied pressure should never be greater than the diastolic blood pressure, to prevent arterial compression.) Venous outflow is enhanced not only by the pressure gradient along the leg, but also by the pumping action of the sequential bladder inflations.

The IPC method can be as effective as anticoagulant prophylaxis (36), and it also adds to the effectiveness of anticoagulant regimens (37). Therefore, it is no surprise that IPC is the standard method of mechanical prophylaxis in hospitalized patients. There are, however, a few shortcomings: i.e., the inflatable bladders restrict mobility and can macerate the skin, and the

repeated inflation and deflation of the bladders is often annoying for awake patients. Therefore, IPC should be discontinued as soon as it is no longer necessary.

Inferior Vena Cava Filters

Inferior vena cava (IVC) filters do not prevent deep vein thrombosis (DVT), but they reduce the risk of pulmonary embolism (by trapping thrombi that break loose from DVT in the legs). These devices are occasionally used in patients with DVT who cannot be anticoagulated, but otherwise they are not recommended for VTE prophylaxis. IVC filters are described in Chapter 22.

WHICH REGIMEN FOR WHICH PATIENT?

The following is a description of the recommended prophylactic regimens for specific clinical settings. Most of these recommendations are taken from the clinical practice guidelines listed at the end of the chapter (2–9). (When guidelines differ in their recommendations, the most recent guideline is usually chosen.) Please note the following specifics for these recommendations: (a) High-risk patients are those with a prior history of VTE, genetic risk factors for VTE, cancer, or multiple risk factors (e.g., advanced age, obesity, heart failure with leg edema); (b) The low-molecular-weight heparin (LMWH) is enoxaparin.

Special Circumstances

The following recommendations apply to all groups of patients or clinical settings:

. For patients with renal failure (creatinine clearance <15 mL/min), the only anticoagulants that can be used are unfractionated heparin (UFH) and coumadin.

. For patients with morbid obesity (BMI > 40 kg/m^2), consider adjusting the dose of the heparins (UFH and LMWH), as shown in Table 5.2.

. For patients with suspected heparin-induced thrombocytopenia (HIT), or a prior history of HIT, fondaparinux can be used for prophylaxis (and has been used in confirmed cases of HIT).

Major General Surgery

. The most recent guidelines recommend UFH or LMWH, with intermittent pneumatic compression (IPC) added in high-risk patients (2). Higher doses of UFH (5,000 units every 8 hours) and LMWH (enoxaparin, 30 mg twice daily) are popular for high-risk patients.

. Prophylaxis can be started preoperatively, but the last doses of UFH and LMWH should be at least 6 hrs and 12 hrs (respectively) before the surgical procedure. Postoperative prophylaxis can begin 6 hours after surgery for UFH, and 12 hours after surgery for LMWH.

. Prophylaxis is generally continued until full ambulation or hospital discharge, but for cancer surgery involving the abdomen and pelvis in high-risk patients, extended prophylaxis (with LMWH) for up to 4 weeks is favored (10).

Bariatric Surgery

- The American Society for Metabolic and Bariatric Surgery favors LMWH plus IPC for prophylaxis, with an enoxaparin dose of 40 mg twice daily for a BMI of 30–49 kg/m^2, and 60 mg twice daily for a BMI ≥ 50 kg/m^2 (3).
- Following bariatric surgery, about 80% of postoperative VTEs occur after hospital discharge (3), so extended prophylaxis (with LMWH) is recommended for a total of about 2 weeks (3). (The duration of prophylaxis has not been adequately studied.)

Orthopedic Surgery

- For hip or knee replacement surgery, a DOAC (dabigatran, rivaroxaban, or apixaban) is favored over LMWH (2), with IPC added in the early postoperative period.
- For hip *fracture* surgery, LMWH is recommended (2,5). (DOACs have not been adequately studied in hip fracture surgery.)
- For major surgery involving the hip and knee, extended prophylaxis is recommended for up to 35 days after the procedure (2,5).

Neurosurgery

- For major neurosurgical procedures, mechanical prophylaxis with IPC is recommended.
- When the risk of postoperative bleeding has subsided, LMWH is added for high-risk patients, and for cancer-related surgery (2).

Cardiac Surgery

- For uncomplicated cases of cardiac surgery, mechanical prophylaxis with IPC is recommended (2,5).
- For complicated cardiac surgery, or high-risk patients, LMWH is added to IPC (5).

Major Trauma

- For solid organ injury or trauma to the extremities, prophylaxis with LMWH (enoxaparin at a dose of 40 mg SC every 12 hrs) should be started when bleeding is not a concern, optimally 12–24 hours after the injury, and mechanical prophylaxis with IPC (if tolerated) is added in high-risk patients (6).
- For traumatic brain injury, mechanical prophylaxis with IPC is used until the CT scan shows no bleeding, or progression of bleeding for 24 hours, then LMWH is added (enoxaparin at a dose of 30 mg SC every 12 hrs).
- For spinal trauma, prophylaxis with LMWH (enoxaparin at a dose of 30 mg SC every 12 hrs) should be started as soon as anticoagulation is considered safe, while mechanical prophylaxis with IPC should be started as soon as possible, and continued along with the LMWH (6).
- Monitoring anti-Xa levels is recommended in major trauma because of frequent variations in renal function.

Acute Medical Illness

. For high-risk patients with an acute medical illness (including all ICU patients), prophylaxis with LMWH is recommended, without adding mechanical prophylaxis (7). Extended prophylaxis after hospital discharge is not recommended (7).

A FINAL WORD

Riddle Me This

> If immobility is a risk factor for deep vein thrombosis (DVT),
> then why isn't DVT rampant in elderly nursing home residents
> who are bed-bound with leg contractures, and why isn't
> perpetual DVT prophylaxis used in people with paraplegia?

The perception that immobility or prolonged bed rest is a risk factor for DVT is an offshoot of Virchow's Triad, which identifies venous stasis as one of the principal risk factors for thrombosis. However, immobility is not necessarily venous stasis. The cardiovascular system is a closed system, and according to the law of conservation of energy and matter, the volumetric flow will be the same in all regions of a closed system. So if the cardiac output is normal, the arterial and venous flows will be the same (cardiac output equals venous return) and there will be no venous stasis with immobility or prolonged bed rest.

What triggers DVT in many of the high-risk hospitalized patients is probably inflammation (other than vascular injury in trauma and orthopedic patients), since the inflammatory and coagulation systems are closely linked. This would explain why in cases of spinal cord injury that result in paraplegia, the risk of DVT is high only for 3–4 weeks following the injury. Thereafter, thromboprophylaxis is discontinued, which implies that prolonged immobility alone is not a risk factor for DVT.

Why is this important? Because the perception that immobility predisposes to DVT is very likely a source of excessive use of anticoagulants for thromboprophylaxis.

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Chapter 6

Analgesia and Sedation in the ICU

To cure sometimes, to relieve often, and to comfort always.

Edward Livingston Trudeau, MD (1848−1915)

Contrary to popular perception, our principal function is not to save lives (since this is impossible on a consistent basis), but rather to *relieve pain and suffering*, and the ICU is the flagship of pain and suffering in hospitalized patients. In surveys of patients who have been discharged from the ICU, anxiety and unrelieved pain are the dominant recollections of the ICU stay (1). While it is not possible to completely eliminate the unpleasantness of the ICU stay, attention to patient comfort is always warranted, and surveys like one in Figure 6.1 (2) indicate that there is much work to be done.

This chapter describes the pharmacological approach to pain and stress relief in the ICU, with a focus on intravenous drug regimens and recommendations from expert commentaries on the subject (3−7). Nonpharmacological measures are not included here, but are available in a clinical practice guideline listed at the end of the chapter (4).

THE ICU EXPERIENCE

It is axiomatic to state that the ICU stay is a stressful experience for patients. Several stressors have been identified, including unrelieved pain and anxiety, dyspnea, the inability to communicate (in intubated patients), and disrupted sleep. The stress of a prolonged ICU stay can have far-reaching neuropsychiatric consequences, as post-traumatic stress disorder has been reported in patients who required prolonged periods of mechanical ventilation (8).

Pain in The ICU

Unrelieved pain is the most frequently cited stressor in the ICU (9), and the frequency of painful experiences is equivalent in surgical and medical ICUs (10).

Altered Pain Perception

Pain is generally defined as an unpleasant sensory experience (11). The degree of this unpleasantness (i.e., pain intensity) varies with the type and strength of the *nociceptive* (pain

producing) stimulus, and is also influenced by the presence and severity of disease. This latter condition applies to critically ill patients, as summarized in the following statements:

. The sensation of pain is magnified in critically ill patients, and this condition of *hypernociception* can transform a minor event into a painful experience.

. A common source of pain in ICU patients is the simple act of being turned in bed (9), and about 50% of patients experience pain at rest (usually in the lower back and legs), in the absence of a noxious stimulus (4,9,10).

. The heightened pain sensation in critically ill patients is attributed to systemic inflammation (via the production of prostenoids) and prolonged immobility.

Failure to recognize the exaggerated pain sensation in ICU patients is a source of inadequate pain control. However, this can be corrected with the use of pain assessment tools, like the ones described next.

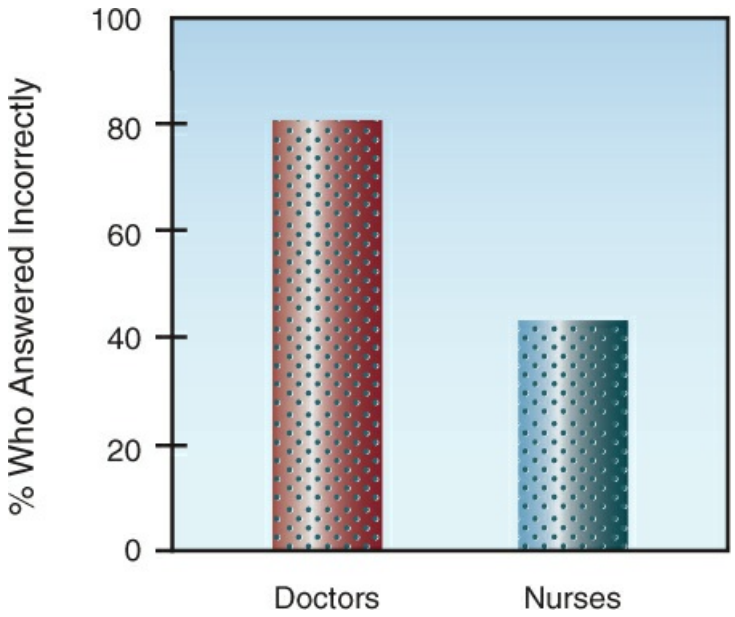

FIGURE 6.1 Percentage of resident physicians and ICU nurses who answered incorrectly when asked if diazepam (Valium) relieves pain.

Monitoring Pain

Routine assessments of pain intensity can be used to guide analgesic therapy. Because pain is a subjective sensation, the patient's self-assessment is the most accurate measure of pain intensity.

. When patients are capable of self-assessment, the *Numerical Ranking Scale* is recommended to quantify pain intensity (4). This is a horizontal scale with 10 equally spaced divider markings, numbered 1 (no pain) to 10 (maximum pain). The patient points to the numbered marking that corresponds to the intensity of pain. A score greater than 3 indicates unacceptable pain.

. When patients are not capable of self-assessment due to heavy sedation (e.g., during assisted ventilation), then physical signs can be used to assess pain. This is the basis for the *Behavioral Pain Scale* shown in Table 6.1 (12), which includes 12 individual behaviors separated into

three categories: facial expression, arm flexion, and tolerance of mechanical ventilation. The final score ranges from 3 (no pain) to 12 (maximum pain). A score of 6 or higher indicates unacceptable pain.

Vital Signs

There is a tendency to look for changes in heart rate or blood pressure as evidence of pain, but this practice should be abandoned, because there is a poor correlation between pain intensity (as reported by patients) and changes in any of the vital signs (3,4).

TABLE 6.1 The Behavioral Pain Scale

Item	Description	Score
Facial Expression	• Relaxed • Partially tightened • Fully tightened • Grimacing	1 2 3 4
Upper Limbs	• No movement • Partially bent • Fully bent, fingers flexed • Permanently retracted	1 2 3 4
Compliance with Ventilation	• Tolerating ventilator • Coughing, but tolerating ventilator • Fighting ventilator • Unable to control ventilation	1 2 3 4
	Total Score	

Score	Interpretation
3	No Pain
≥6	Unacceptable pain
12	Maximal pain

From Reference 11.

ANALGESIA WITH OPIOIDS

The drugs described in this section are the most effective analgesics available (and hence the most popular drugs used for pain relief in the ICU). At the outset, a few definitions deserve mention:

. An *opiate* is a natural chemical derivative of opium.

. An *opioid* is a naturally-occurring or synthetic derivative of opium that acts by stimulating specific receptors (called *opioid receptors*) in the central nervous system and elsewhere. Stimulation of opioid receptors produces a variety of effects, including analgesia, sedation, euphoria, pupillary constriction, respiratory depression, bradycardia, constipation, nausea and vomiting, urinary retention, and pruritis.

. A *narcotic* is an outdated term for an opioid, but it has also been adopted by law enforcement agencies to refer to an opioid that is obtained illegally and used for non-medical purposes.

The terms opiate and opioid are often used interchangeably, but opioid is used here because it is a more accurate term for the drugs included in this section. In addition to their analgesic effects, opioids have the added benefit of producing mild sedation, but without amnesic effects (13). All opioids are metabolized in the liver, and the metabolites are excreted in the urine.

Drugs and Dosing Regimens

The opioids used most frequently in the ICU are morphine, fentanyl, and hydromorphone, and the recommended intravenous dosing for each drug is shown in Table 6.2 (3). It is important to emphasize that opioid dose requirements can vary widely in individual patients, and therefore *the effective dose of an opioid is determined by each patient's response, and not by the recommended dosing of the drug*.

TABLE 6.2 Commonly Used Intravenous Opioids

	Morphine	Hydromorphone	Fentanyl
Onset	5–10 min	5–15 min	1–2 min
Bolus Dosing	2–4 mg q 1–2 hr	0.2–0.6 mg q 1–2 hr	0.35–0.5 µg/kg q 0.5–1 hr
Infusion Rate	2–30 mg/hr	0.5–3 mg/hr	0.7–10 µg/kg/hr
PCA Demand (bolus) Lockout Interval	0.5–3 mg 10–20 min	0.1–0.5 mg 5–15 min	15–75 µg 3–10 min
Lipid Solubility	x	0.2x	600x
Active Metabolites	Yes	Yes	No
Histamine Release	Yes	No	No
Dose Adjustment for Renal Failure	↓ 50%	None	? Avoid†

Dosing recommendations from Reference 3. †From Reference 5.

Morphine

Morphine is the principal alkaloid of opium, and has been the traditional opioid used for pain control in the ICU. However, morphine has the following disadvantages that have curbed its popularity:

. Morphine has active metabolites that accumulate in renal failure. One metabolite (morphine 3-glucuronide) can produce agitation with myoclonus and seizures (14), while another metabolite (morphine-6-glucuronide) has more potent analgesic effects than the parent drug (15). To avoid accumulation of these metabolites, *the maintenance dose of morphine should be reduced by 50% in patients with renal failure* (16).

. Morphine promotes the release of histamine, which produces systemic vasodilation and a decrease in blood pressure (17). Hypotension is typically seen in patients with a

hyperadrenergic state and increased peripheral vascular tone (3). Morphine-induced histamine release does not promote bronchoconstriction, as morphine doses of 1.5 mg/kg have been given to asthma patients without adverse consequences (18).

Fentanyl

Fentanyl is a synthetic opioid that has replaced morphine as the most popular opioid analgesic in ICUs (9). The advantages of fentanyl over morphine include the following:

. Fentanyl is 600 times more lipid soluble than morphine, and has a more rapid onset of action.

. Fentanyl does not promote histamine release (17), and thus has less risk of hypotension than morphine. The hemodynamic tolerance to fentanyl is a major source of its appeal in critically ill patients.

. Fentanyl has no active metabolites. (However, the parent drug can accumulate in renal failure, and some recommend avoiding fentanyl in patients with end-stage renal disease) (5).

One disadvantage of fentanyl is its lipophilicity, which promotes accumulation in the brain with continued usage.

Hydromorphone

Hydromorphone (Dilaudid®) is a semi-synthetic derivative of morphine that may produce more effective analgesia than morphine (19), and does not require dose alteration in renal failure. It seems to be favored for the treatment of cancer-related pain, but has no proven advantages over fentanyl for analgesia.

Remifentanil

Remifentanil is an ultra-short acting opioid that is 250 times more potent than morphine (6). The recommended intravenous dose begins with a loading dose of 1.5 µg/kg, and follows with a continuous infusion at 0.5–15 µg/kg/hr (3). Analgesic effects appear in about one minute, and are lost within 10 minutes after stopping the infusion. The short duration of action is a reflection of drug metabolism; i.e., remifentanil is broken down by nonspecific esterases in plasma (6). Since drug metabolism does not take place in the liver or kidneys, dose adjustments are not necessary in renal or hepatic failure.

Remifentanil has not been a popular drug for pain control in ICUs, but it has been used in patients with traumatic brain injury (20), where its short duration of action allows for frequent evaluations of neurologic status. The abrupt cessation of opioid activity can precipitate acute opioid withdrawal (6), which can be prevented by combining remifentanil with a longer-acting opioid.

Meperidine

Meperidine (Demerol®, Pethidine®) is an opioid analgesic that is no longer favored for pain control in the ICU because of the potential for *neurotoxicity*. Meperidine is metabolized in the liver to normeperidine, a metabolite that is slowly excreted by the kidneys (elimination half-life is 15–40 hours). Accumulation of normeperidine can produce central nervous system excitation, with agitation, myoclonus, delirium, and generalized seizures (21). Since renal dysfunction is

prevalent in ICU patients, accumulation of normeperidine is an unacceptable risk.

Patient-Controlled Analgesia

For patients who are awake and capable of drug self-administration, *patient-controlled analgesia* (PCA) can be an effective method of pain control, and may be superior to intermittent opioid dosing. The PCA method uses an electronic infusion pump that can be activated by the patient. When pain is sensed, the patient presses a button connected to the pump to receive a small intravenous bolus of drug. After each bolus, the pump is disabled for a mandatory time period called the *lockout interval*, to prevent overdosing. The opioid dosing regimens for PCA are shown in Table 6.2. The minimum lockout interval is determined by the time required to achieve peak drug effect (22). When writing orders for PCA, you must specify the initial loading dose (if any), the lockout interval, and the repeat bolus dose. PCA can be used alone or in conjunction with a low-dose opioid infusion.

Adverse Effects of Opioids

Opioids can produce a multitude of adverse effects;, and the following are the ones of most concern in ICU patients. (See also Chapter 52 for a description of opioid overdoses.)

Respiratory Depression

Opioids produce a centrally-mediated, dose-dependent decrease in respiratory rate and tidal volume, but *respiratory depression and hypoxemia are uncommon when opioids are given in the usual doses* (23). However, opioid doses that impair arousal can impair ventilation and promote hypercapnia (24). Patients with sleep apnea syndrome or chronic hypercapnia are particularly prone to respiratory depression from opioids.

Cardiovascular Effects

Opioid analgesia is often accompanied by decreases in blood pressure and heart rate, which are the result of decreased sympathetic activity and increased parasympathetic activity. (Morphine-induced hypotension may also be the result of histamine release.) Opioid effects on blood pressure are usually mild and well-tolerated, at least in the supine position (25). Decreases in blood pressure can be pronounced in patients with hypovolemia or heart failure (where there is an increased baseline sympathetic tone), or when opioids are given in combination with benzodiazepines (26). Opioid-induced hypotension is rarely a threat to tissue perfusion, and the blood pressure responds to intravenous fluids or small bolus doses of vasopressors.

Intestinal Motility

Opioids are well known for their ability to depress bowel motility via activation of opioid receptors in the GI tract. This is a source of troublesome constipation in cancer patients; in critically ill patients, impaired GI motility can promote reflux of enteral tube feedings into the oropharynx, creating a risk for aspiration pneumonia.

METHYLNALTREXONE: Methylnaltrexone is a peripheral opioid receptor antagonist that can block the GI effects of opioids without influencing the analgesic effects. This drug has proven successful in treating opioid-induced constipation in palliative care settings, but a preliminary

study in ICU patients is not encouraging (27). In this study, intravenous methylnaltrexone in a dose of 12 mg daily (in adults weighing >60 kg) did not significantly increase laxation in patients with opioid-induced constipation.

Nausea and Vomiting

Opioids can promote vomiting via stimulation of the chemoreceptor trigger zone in the lower brainstem (24). All opioids are equivalent in their ability to promote vomiting, but vomiting induced by one opioid occasionally resolves when another opioid is used.

ANALGESIA WITH NON-OPIOIDS

Recent concerns about the rise in opioid dependency have prompted recommendations to reduce opioid use in hospitalized patients, if possible. To this end, the following analgesic agents should be considered as first-line agents or adjuvants to opioid analgesia in the ICU. The intravenous dosing regimens for these agents are presented in Table 6.3.

TABLE 6.3 Intravenous Non-Opioid Analgesia

Drug	Dosing Regimens and Comments
Acetaminophen	Dosing: 1 gram IV every 6 hr. Daily dose should not exceed 4 grams. Comment: Has no anti-inflammatory activity.
Ketorolac	Dosing: 30 mg IV every 6 hrs. Reduce dose by 50% for patients with renal failure, age ≥65 yrs, or body weight <50 kg. Comment: Serious complications (e.g., renal impairment) are uncommon with short-term use.
Ketamine	Dosing: 60–120 µg/hr, in combination with an opioid. Comment: Psychomimetic effects are not prominent at the doses used for opioid-sparing analgesia.

Acetaminophen

Acetaminophen was approved for intravenous use in 2010, and is intended for the short-term treatment of pain and fever in postoperative patients who are unable to receive the drug via the oral or rectal routes. The recommended dose is 1 gram IV every 6 hrs, with a maximum allowable dose of 4 grams daily (to prevent acetaminophen hepatotoxicity) (28). This dosing regimen has a documented opiate-sparing effect in postoperative patients (29). The major disadvantage of acetaminophen (in addition to the risk of hepatotoxicity) is the lack of an anti-inflammatory effect.

Ketorolac

Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) that produces analgesia without respiratory depression. The drug can be used alone for mild pain, but is more often used in combination with an opioid analgesic for moderate-to-severe pain. Ketorolac co-administration can reduce the opioid dose by 25−50% (30).

Dosing Regimen

Ketorolac can be given by intravenous (IV) or intramuscular (IM) injection, but IM injections of ketorolac can produce hematomas (31), so the IV route is preferred. The recommended dosing regimen for moderate-to-severe pain is 30 mg IV every 6 hrs (32). A 50% dose reduction (15 mg every 6 hrs) is recommended for patients with renal impairment, advanced age, and for those with a body weight <50 kg (32).

Risk

The beneficial actions of ketorolac and other NSAIDs are attributed to inhibition of prostaglandin production, but this also creates a risk for gastric mucosal injury and impaired renal function. These adverse effects are typically associated with excessive dosing or prolonged exposure to NSAIDs, and they are uncommon with short-term ketorolac use in the recommended doses (32–34).

Ketamine

Ketamine is a phencyclidine (PCP!) derivative that has anesthetic and analgesic properties, but it also has psychomimetic effects (e.g., dissociative reactions, hallucinations, and delirium after discontinuation), and these latter effects have limited its use as an analgesic outside the operating room. However, low doses of ketamine (60–120 μg/kg/hr) have been used in combination with opioids (opioid-sparing effect) without troublesome psychomimetic side effects (6).

Other notable effects of ketamine include increases in blood pressure and heart rate (sympathomimetic effects), bronchodilation, nausea and vomiting, and hypersalivation (6). The sympathomimetic effects may be advantageous in patients with circulatory shock, while the bronchodilation is desirable in patients with asthma. However, the non-analgesic effects of ketamine are diminished in the dose range used for opioid-sparing analgesia. Ketamine is generally not advised for patients with myocardial ischemia (6).

Neuropathic Pain

Non-opioid analgesia is usually required for neuropathic pain (e.g., from diabetic neuropathy), and the recommended drugs for this type of pain are *gabapentin* and *carbamazepine* (3). Both drugs must be given enterally. Effective drug doses vary in individual patients, but typical doses are 600 mg every 8 hrs for gabapentin, and 100 mg every 6 hours for carbamazepine.

ANXIETY IN THE ICU

Anxiety and related disorders (agitation and delirium) are observed in as many as 85% of patients in the ICU (35). These disorders can be defined as follows:

. *Anxiety* is characterized by exaggerated feelings of fear or apprehension that are sustained by internal mechanisms more than external events.

. *Agitation* is a state of anxiety that is accompanied by increased motor activity.

. *Delirium* is an acute confusional state that may, or may not, have agitation as a component. Although delirium is often equated with agitation, there is a hypoactive form of delirium that is

characterized by lethargy. (Delirium is described in more detail in Chapter 45.)

The common denominator in these disorders is the *absence of a sense of well-being*.

Sedation

Sedation is the process of relieving anxiety and establishing a state of calm. This process includes general supportive measures (like frequent communication with patients and families), and drug therapy. Several drugs are available for sedation in ICU patients, including benzodiazepines (e.g., midazolam), propofol, dexmedetomidine, and haloperidol.

Monitoring Sedation

The routine use of sedation scales is instrumental in achieving effective sedation in the ICU. The sedation scales that are most reliable for ICU patients are the Sedation-Agitation Scale (SAS) and the Richmond Agitation-Sedation Scale (RASS) (3), which is shown in Table 6.4 (36). The RASS includes 4 possible scores for progressive agitation (+1 to +4) and 5 possible scores for progressive sedation (–1 to –5). The optimal RASS score is zero (alert and calm). The added advantage of RASS is the ability to monitor serial changes in a patient's mental state (37). This latter feature allows the RASS score to be used as the end-point of sedative drug therapy. (Sedative drug infusions can be titrated to achieve a RASS score of –1 to –2, which represents light sedation.)

TABLE 6.4 The Richmond Agitation-Sedation Scale

Score	Term	Description
+4	Combative	Overly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s), catheter(s), or aggressive behavior
+2	Agitated	Frequent non-purposeful movement or patient-ventilator asynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert & calm	
−1	Drowsy	Not fully alert, but awakens for >10 sec, with eye contact, to voice
−2	Light sedation	Briefly awakens (<10 sec), with eye contact to voice
−3	Moderate sedation	Any movement (but no eye contact) to voice
−4	Deep sedation	No response to voice, but movement to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

To determine the RASS, proceed as follows:

Step 1 Observation: Observe the patient without interaction. If patient is alert, assign the appropriate score (0 to +4). If patient is not alert, go to Step 2.

Step 2 Verbal Stimulation: Address the patient by name in a loud voice and ask the patient to look at you. Can repeat once if necessary. If patient responds to voice, assign the appropriate score (−1 to −3). If there is no

response, go to Step 3.

Step 3 Physical Stimulation: Shake the patient's shoulder. If there is no response, rub the sternum vigorously. Assign the appropriate score (−4 to −5).

From Reference 36.

BENZODIAZEPINES

Benzodiazepines have been the traditional sedative agents used in the ICU, but they are gradually losing ground to other sedatives because of drug accumulation with prolonged use, and an increased risk of ICU-related delirium (see later). There are two benzodiazepines that are favored for intravenous delivery: midazolam (Versed®) and lorazepam (Ativan®). Diazepam (Valium®) is generally avoided because the long half-life (90 hours) and presence of active metabolites promotes prolonged sedation, especially with renal impairment. The intravenous dosing regimens for midazolam and lorazepam are shown in Table 6.5 (3).

Midazolam

Midazolam is a short-acting drug that is favored for procedural sedation. Sedative effects are apparent within 5 minutes, and they last for 1–2 hours. Because of the short-lived effect, midazolam can be given as a continuous IV infusion for more prolonged sedation. However, midazolam is highly lipid soluble, and will accumulate in the central nervous system when infused continuously. To avoid prolonged sedation from drug accumulation, *midazolam infusions should be limited to ≤48 hrs* (4).

Midazolam is metabolized by the cytochrome P450 enzyme system in the liver, and drugs that interfere with this enzyme system (e.g., diltiazem, erythromycin) can potentiate the sedative effects. Midazolam has one active metabolite that is cleared by the kidneys, and renal impairment can add to the tendency for prolonged sedation (3,4).

Lorazepam

Lorazepam has a rapid onset of action, like midazolam, but the effect lasts longer (up to 6 hours). Continuous infusions of lorazepam can also lead to drug accumulation and prolonged sedation, but this effect is less pronounced (38), because lorazepam is less lipid soluble than midazolam, and has no active metabolites. However, there is a more serious risk associated with lorazepam infusions: i.e., propylene glycol toxicity (see next).

Propylene Glycol Toxicity

Propylene glycol is added to certain intravenous drug preparations to enhance drug solubility in plasma, and intravenous lorazepam has the highest concentration of propylene glycol of all drug preparations. Propylene glycol is converted to lactic acid in the liver, and excessive intake can produce a clinical syndrome characterized by a metabolic (lactic) acidosis, altered mentation, systemic inflammation, and renal failure (39). The risk of this "toxidrome" emerges when the lorazepam infusion rate exceeds the upper limit of the recommended rate (0.1 mg/kg/hr), or is >10 mg/hr, for longer than 48 hours (39,40).

TABLE 6.5 Sedation with Intravenous Benzodiazepines		
Feature	**Midazolam**	**Lorazepam**
Bolus Dose	0.01–0.05 mg/kg	0.02–0.04 mg/kg
Onset of Action	3–5 min	5–15 min
Duration	1–2 hr	2–6 hr
Continuous Infusion	0.02–0.1 mg/kg/hr	0.01–0.1 mg/kg/hr
Lipid Solubility	+++	++
Concerns	Active Metabolites	Propylene Glycol Toxicity

Dosing recommendations from Reference 3.

OSMOLAL GAP: Plasma levels of propylene glycol are not routinely available, but an elevated osmolal gap (i.e., >10 mosm/kg H_2O) has shown a good correlation with propylene glycol accumulation (41). (Lactate levels are unreliable for predicting either propylene glycol levels or the risk of clinical symptoms.) Therefore, monitoring the osmolal gap is recommended when the lorazepam infusion rate is ≥0.1 mg/kg hr, or >10 mg/hr, for 48 hours (39–41). (See Chapter 31 for more on the osmolal gap, and how to calculate the plasma osmolality.)

Advantages

The advantages of sedation with benzodiazepines include the following:

. The rapid onset of action makes benzodiazepines well-suited for the acute management of anxiety and agitation.

. Benzodiazepines cause a dose-dependent anterograde amnesia that is distinct from the sedative effect (42). Short-term memory is less affected than long-term memory. This is considered advantageous because it eliminates memories of stressful experiences, and it may explain why as many as 40% of patients who leave the ICU have no recollection of events that occurred while in the ICU (1,43).

. Benzodiazepines are the sedatives of choice for the management of alcohol and opioid withdrawal.

Disadvantages

The major disadvantages of benzodiazepines are drug accumulation with prolonged use, and a perceived tendency to promote delirium.

Prolonged Sedation

The major disadvantage of benzodiazepines is their tendency to accumulate and produce excessive sedation and delayed awakening, which can delay weaning from mechanical ventilation and prolong the ICU stay. As mentioned earlier, this is more of a problem with midazolam than lorazepam; e.g., in one study of prolonged sedation in ventilator-dependent patients, the time to emerge from sedation was 30 hours for midazolam and 4–5 hours for

lorazepam (38). Lorazepam is thus the benzodiazepine-of-choice for prolonged periods of continuous-infusion sedation (e.g., in ventilator-dependent patients) (4).

Delirium

Clinical studies have shown a relationship between benzodiazepine use and delirium in ICU patients (4,44). The link may be gamma-amino-butyric-acid (GABA), the principal inhibitory neurotransmitter in the brain; i.e., benzodiazepines act by binding to GABA receptors in the brain, and GABA-mediated neurotransmission is also involved in the development of delirium (44). This is supported by evidence that sedation with drugs that do not involve GABA receptors is less likely to be accompanied by delirium (44).

Preventive Measures

The following strategies are available for reducing the risks of oversedation and/or delirium associated with the prolonged use of benzodiazepines:

. Daily interruption of benzodiazepine infusions, known as a "sedation holiday", is an effective measure to hasten weaning from mechanical ventilation (4,45).

. Maintaining light sedation by titrating benzodiazepine dosing to a specific target on one of the sedation scales has been shown to promote weaning from mechanical ventilation and reduce the risk of delirium (4,44).

. Avoiding benzodiazepines for prolonged sedation during mechanical ventilation, if possible, is the recommendation of the most recent guidelines on sedation in the ICU (4).

SEDATION WITH RAPID-AROUSAL AGENTS

Concerns about the risks associated with benzodiazepines has prompted a shift in attention to two agents that allow rapid arousal from sedation: propofol and dexmedetomidine.

Propofol

Propofol (Deprivan®) is a rapidly-acting, GABAergic sedative that was introduced for the induction of general anesthesia, and has subsequently become a popular agent for sedation during mechanical ventilation. A profile of this drug is presented in Table 6.6

TABLE 6.6 Sedation with Rapid Arousal Agents

Feature	Propofol	Dexmedetomidine
Loading Dose	5 µg/kg/min over 5 min	1 µg/kg over 10 min
Onset of Action	1−2 min	5−10 min
Maintenance Infusion	5−50 µg/kg/min	0.2–1.5 µg/kg/hr
Time to Arousal	10−15 min†	6−10 min
Respiratory Depression	Yes	No

Adverse Effects	• Hypotension • Hyperlipidemia • Propofol Infusion Syndrome	• Hypotension • Bradycardia

†Arousal time is influenced by depth of sedation and duration of the infusion (see Table 6.7). Dosing recommendations from Reference 3.

Actions

Propofol has sedative, amnesic, and anticonvulsant effects, but no analgesic effects (46). A single intravenous bolus produces sedation within 1–2 minutes, and the drug effect lasts 5–8 minutes (46). Prolonged sedation requires a continuous drug infusion, and termination of the infusion can lead to arousal in only 10–15 minutes (46). However, the arousal time is dependent on the depth of sedation and the duration of the continuous infusion. This is demonstrated in Table 6.7, which shows the arousal times in ICU patients who were maintained at different levels of sedation (light or deep sedation) during propofol infusions that varied from one day to 14 days (47). Note that arousal times were longer with deep sedation and longer infusion times, and that the depth of sedation had the most profound effect on the time to arousal. These result highlight the importance of maintaining light sedation with propofol (if possible) to ensure more rapid emergence from sedation.

Preparation and Dosage

Propofol is suspended in a 10% lipid emulsion to enhance solubility in plasma. This lipid emulsion is almost identical to the 10% lipid formulation used in parenteral nutrition formulas, and it has a caloric density of 1 kcal/mL (which should be included as part of the daily caloric intake). *Propofol dosing is based on ideal rather than actual body weight*, and no dose adjustment is required for renal failure or hepatic insufficiency (46).

Adverse Effects

The most common side effects of propofol are respiratory depression and hypotension (5,48). The risk of respiratory depression mandates that only patients receiving mechanical ventilation can be sedated with propofol. The hypotension is attributed to systemic vasodilation (5), and can be profound in conditions like hypovolemia and heart failure, where blood pressure is maintained by systemic vasoconstriction. Loading doses of propofol are not advised in patients who are hemodynamically unstable (3).

Other notable consequences of propofol sedation include hypertriglyceridemia (attributed to the lipid emulsion used to deliver the drug) (48), necrotizing pancreatitis (rare) (49), anaphylactoid reactions (uncommon), a greenish hue in urine (from harmless phenolic metabolites) (46), and the life-threatening condition described next.

PROPOFOL INFUSION SYNDROME: Propofol infusion syndrome is an uncommon condition characterized by the abrupt onset of systolic heart failure, unrelenting lactic acidosis, rhabdomyolysis, acute renal failure, and eventual multiorgan failure (50). The etiology is unclear, but may be the result of propofol-induced inhibition of the mitochondrial electron transport chain (which produces high-energy ATP molecules). This syndrome typically occurs during high-dose propofol infusions (>80 µg/kg/min, or >5 mg/kg/hr) for longer than 48 hours (51), but it has also been reported at moderate infusion rates (36 µg/kg/min) (52). The prevalence

of this condition is unclear, since many of the manifestations are shared by other severe illnesses, but an incidence of 3% has been reported (52). Management involves general supportive care, and ECMO has been used in a few cases (50). The mortality rate is 30–35% (52,53).

TABLE 6.7 Factors that Influence Emergence from Propofol Sedation

Infusion Time	Arousal Time	
	Light Sedation	Deep Sedation
24 hours	13 minutes	25 hours
72 hours	34 minutes	59 hours
7 days	3.3 hours	71 hours
14 days	3.4 hours	74 hours

From Reference 47.

Dexmedetomidine

Dexmedetomidine (Precedex®) is an alpha-2 adrenergic agonist that has sedative, amnesic, and mild analgesic effects, and does not depress ventilation (54). A brief profile of the drug is presented in Table 6.6. The most distinguishing feature of dexmedetomidine is the type of the sedation it produces, which is described next.

Cooperative Sedation

The sedation produced by dexmedetomidine is unique because *arousal is maintained, despite deep levels of sedation*. Patients can be aroused from sedation without reducing or halting the drug infusion, and when arousal is no longer necessary, the patient will spontaneously return to the prior state of sedation. This has been called *cooperative sedation* (6), and it is more like a sleep state than the drug-induced stupor produced by the benzodiazepines and propofol. In fact the EEG changes in dexmedetomidine-induced sedation are similar to the changes that occur in natural sleep (6).

Advantages

Sedation with dexmedetomidine is well-suited for situations where temporary arousal is desirable, such as weaning attempts during mechanical ventilation, or periodic evaluations of mental status in stroke or traumatic brain injury. Other advantages include the following:

. Sedation with dexmedetomidine obviates the need for periodic or daily interruption of sedative infusions (the sedation holiday), thereby allowing patients to be maintained at constant level of sedation.

. Since dexmedetomidine does not depress ventilation, it can be used in patients who are not ventilator-dependent.

. The analgesic effects of dexmedetomidine can be advantageous for reducing opioid requirements (opioid sparing effect).

. Delirium is less frequent with dexmedetomidine compared to benzodiazepines or propofol (55). In addition, dexmedetomidine is the drug-of-choice for the treatment of ICU-related delirium (4). This is a significant advantage for dexmedetomidine, since about 40% of ICU patients above the age of 65 will develop delirium (56).

Because of these advantages, dexmedetomidine is steadily growing in popularity for the sedation of critically ill patients, and it is considered superior to benzodiazepines for sedation during mechanical ventilation (4).

Disadvantages

. Dexmedetomidine produces dose-dependent decreases in heart rate, blood pressure, and circulating norepinephrine levels (sympatholytic effect) (6), and this effect is particularly marked in conditions where heart rate and blood pressure are supported by increased sympathetic activity; e.g., heart failure with reduced ejection fraction (57).

. Dexmedetomidine can have a withdrawal syndrome characterized by signs of sympathetic overactivity (i.e., tachycardia, hypertension, and agitation) (58). Dexmedetomidine withdrawal is reported in 30% of patients (58), and is unrelated to the infusion rate or duration.

ANTIPSYCHOTIC AGENTS

Several antipsychotic agents are used for sedation in hospitalized patients, including Ziprasidone (Geodon®), quetiapine (Seroquel®), risperidone (Risperdal®), and haloperidol (Haldol®). The following presentation focuses on haloperidol, which is the only antipsychotic agent that can be given intravenously, and has a long history of treating agitation and delirium in hospitalized patients.

Haloperidol

Haloperidol is a dopamine receptor antagonist that promotes sedation without troublesome respiratory depression or cardiovascular compromise (although hypotension is a risk in hypovolemic patients) (59). The principal use of haloperidol has been the treatment of agitation and delirium that are not the result of alcohol or drug withdrawal. As mentioned earlier, dexmedetomidine is considered the drug of choice for hospital-related delirium (4), but haloperidol still has a role for patients who do not tolerate dexmedetomidine because of bradycardia or hypotension.

TABLE 6.8 Intravenous Halperidol for Sedation†

1. Begin with 5 mg of haloperidol as an intravenous bolus.
2. For severely agitated or disruptive patients, add midazolam (1 mg) for a more rapid onset of sedation.
3. Wait 15 minutes.
4. If no response, double the dose of haloperidol (10 mg IV).
5. If no response after the second dose, switch to another agent.
6. If the response is satisfactory, maintain sedation with periodic doses of haloperidol (at 25% of the effective dose)

given at 6–hour intervals.

†Do not use if the corrected QT interval (QTc) is >500 msec.

Dosing Recommendations

Haloperidol is given in intravenous bolus doses for the acute management of agitation and delirium. Following a single intravenous dose, the sedative effect begins after 10–20 minutes, and it lasts for 3−4 hours (59).

A dosing regimen for intravenous haloperidol is outlined in Table 6.8. (*Caveat:* Do not use haloperidol if the corrected QT interval (QTc) on the ECG is >500 msec.) The initial dose of haloperidol is typically 5 mg (60). Since haloperidol is not a rapidly-acting drug, midazolam (1−2 mg) can be given with the haloperidol to achieve more rapid control in patients who are severely agitated or disruptive. If the initial dose of haloperidol does not produce the desired level of sedation after 20 minutes, a second dose is given at twice the strength of the initial dose (10 mg). If the second dose of haloperidol is ineffective, then switch to another agent. If the response to haloperidol is satisfactory, then sedation is maintained with periodic doses (at 25% of the effective initial dose) at 4−6 hour intervals (61).

Adverse Effects

The following are the notable risks associated with haloperidol:

. *Extrapyramidal reactions* (e.g., rigidity, spasmodic movements) are dose-related side effects when haloperidol is given orally, but these reactions *are uncommon when haloperidol is given intravenously* (for unclear reasons) (62).

. The most noted risk with haloperidol is prolongation of the QT interval on the ECG, which can trigger a polymorphic ventricular tachycardia known as *torsade de pointes* (which is described in more detail in Chapter 19). This arrhythmia has been reported in 3–4% of patients who received intravenous haloperidol (63), and most cases occurred when the corrected QT interval (QTc) was >500 msec, or the daily dose of haloperidol exceeded 35 mg. Therefore, a QTc >500 msec is considered a contraindication to intravenous haloperidol.

. One of the more egregious (and often overlooked) complications of haloperidol is the *neuroleptic malignant syndrome*, which is an idiosyncratic reaction that presents with hyperpyrexia, severe muscle rigidity, and rhabdomyolysis. This condition has been reported in ICU patients receiving intravenous haloperidol (64), and it can be fatal if left unnoticed. (See Chapter 43 for a more detailed description of this condition.)

A FINAL WORD

From Opiophobia to Opiophilia, and Back Again

Opiophobia

The term “opiophobia” was introduced in the 1980s (65) to describe the reluctance of physicians to prescribe opioids for pain relief, based on the fear of promoting opioid abuse in the community. The general consensus at that time was that pain was undertreated, and opiophobia

was tagged as the culprit. To correct this, The American Pain Society named pain as the "fifth vital sign" (to increase awareness of untreated pain) (66) and to encourage the use of opioids, emphasis was placed on a single study involving 11,000 patients who received opioids during their hospital stay, which showed that only four of the patients developed an opioid addiction (67). (This study was actually a letter to the editor.)

Opiophilia

The efforts to encourage opioid use that began in the 1990s were a smashing success, and by 2010, opioid prescription hit a peak of 81 prescription for every 100 Americans (68)! This "opiophilia" has, of course, been blamed for the current "epidemic" of opioid abuse and opioid-related deaths. In the twenty years from 1999 to 2019, there were an estimated 500,000 deaths from opioid overdose (69). Of interest, opioid prescribing has declined in recent years, but the opioid death toll continues to rise.

Back to Opiophobia

The current opioid abuse problem has prompted efforts to curb the clinical use of opioids. The aim is to foster a reluctance to prescribe opioids for pain relief, based on the fear of promoting opioid abuse in the community, which is opiophobia (again)! *And so it goes*.

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Section III

PHYSIOLOGICAL MONITORING

Not everything that can be counted counts, and not everything that counts can be counted.

Albert Einstein

Chapter 7

Oximetry and Capnography

The killing vice of a young doctor is intellectual laziness.

Sir William Osler (*a*)

The introduction of optical techniques for the noninvasive and continuous monitoring of oxyhemoglobin saturation in blood (oximetry) and carbon dioxide levels in exhaled gas (capnography) is simply the most useful innovation in critical care monitoring since the advent of intensive care units (in this author's opinion). The reach of "pulse" oximetry has extended beyond the ICU, and even beyond the hospital, with the pulse oximetry measurement being proposed as the fifth vital sign (1), while exhaled CO_2 monitoring has become an indispensable tool for ensuring the safety of procedural sedation, and for predicting the outcome of cardiopulmonary resuscitation.

Despite the ubiquity and promise of pulse oximetry and capnography, there is evidence that the understanding of these techniques is far from satisfactory (2). The information in this chapter should help to correct this deficiency.

OXIMETRY: METHODOLOGY

Molecules absorb light at wavelengths that are specific for each molecule. This is the basis for the technique of *spectrophotometry*, which uses light waves to identify the molecular composition of a medium. The application of this technique to the detection of hemoglobin in its different forms is known as *oximetry*.

Light Absorption by Hemoglobin

Hemoglobin (like all proteins) changes its structural configuration when it participates in a chemical reaction, and each of the hemoglobin configurations has a distinct pattern of light absorption. This is demonstrated in Figure 7.1 (3). Four different forms of hemoglobin are represented: oxygenated hemoglobin (HbO_2) deoxygenated hemoglobin (Hb), methemoglobin (metHb) and carboxyhemoglobin (COHb). In the red region of the light spectrum (represented by the wavelength of 660 nm), oxygenated hemoglobin (HbO_2) does not absorb light as well as deoxygenated hemoglobin (Hb), which is why oxygenated blood is more intensely red than

deoxygenated blood. The opposite is true in the infrared region of the spectrum (represented by the wavelength of 940 nm), where HbO_2 absorbs light more effectively than Hb. Based on these absorption patterns, two wavelengths of light (660 nm and 940 nm) can be used to identify oxygenated and deoxygenated hemoglobin.

Early Oximetry

Oximetry was introduced in the 1940s to detect hypoxemia in fighter pilots. The early use of oximetry involved the transmission of red and infrared light beams through the earlobes, but this methodology had two major shortcomings: (a) the transmission of light was influenced by factors other than hemoglobin (e.g., skin pigments, tissue thickness), and (b) it was not possible to differentiate between the hemoglobin in arteries and veins. As a result of these problems, oximetry failed to gain acceptance as a monitoring tool until the 1970s, when *pulse oximetry* was introduced.

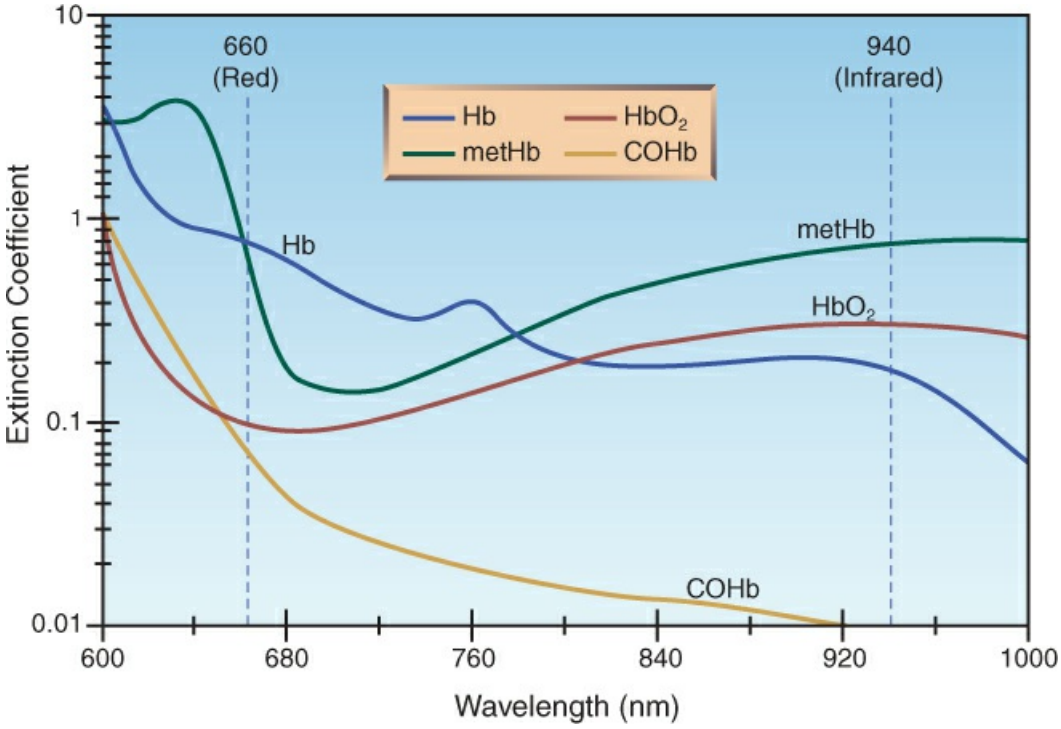

FIGURE 7.1 Light absorption by oxygenated hemoglobin (HbO_2), deoxygenated hemoglobin (Hb), carboxyhemoglobin (COHb), and methemoglobin (metHb) The vertical lines represent the two wavelengths of light (660 nm and 940 nm) used by pulse oximeters. Adapted from Reference 3.

Pulse Oximetry

When a light beam passes through a pulsating artery, the phasic changes in arterial blood volume create pulsatile variations in the intensity of the transmitted light beam. This is demonstrated in the "photoplethysmogram" in Figure 7.2, which shows that the increase in arterial blood volume during systole is associated with a decrease in the transmission of light through the artery. Therefore, restricting the analysis of red and infrared light transmission to the systolic fraction of the photoplethysmogram (A/B in Figure 7.2) will focus the analysis on arterial blood, thereby

reducing or eliminating errors due to light absorption by non-pulsatile elements (e.g., hemoglobin in veins). This is the basic principle for pulse oximetry (3,4).

Fingertip Pulse Oximetry

Pulse oximetry is typically performed with a fingertip probe like the one in Figure 7.3. One side of the probe contains two light-emitting diodes that emit monochromatic light at wavelengths of 660 nm and 940 nm. These light waves pass through the finger and are sensed by a photodetector on the opposite side of the probe. These probes also generate a pulsatile photoplethysmography tracing, which is shown at the bottom of the figure. (Note that the tracing is reversed to resemble an arterial pressure waveform.) The intensity of light transmission during the systolic portion of the photoplethysmography tracing is used as a reflection of the deoxygenated hemoglobin (Hb, at 660 nm) and oxygenated hemoglobin (HbO_2, at 940 nm) in arterial blood. The ratio of HbO_2 to total hemoglobin (HbO_2 + Hb) is then used to define the fraction of hemoglobin that is saturated with oxygen. The resulting "pulse oximeter saturation" (SpO_2) is expressed as a percentage:

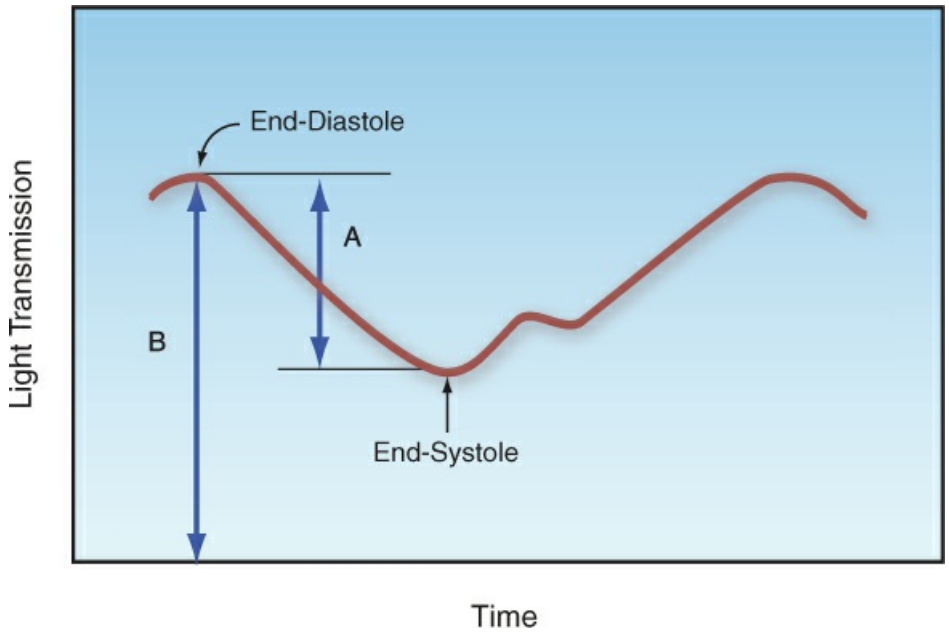

FIGURE 7.2 Photoplethysmography tracing showing the changes in light transmission resulting from the pulsatile change in arterial blood volume. A = systolic amplitude, B = baseline transmission. See text for further explanation.

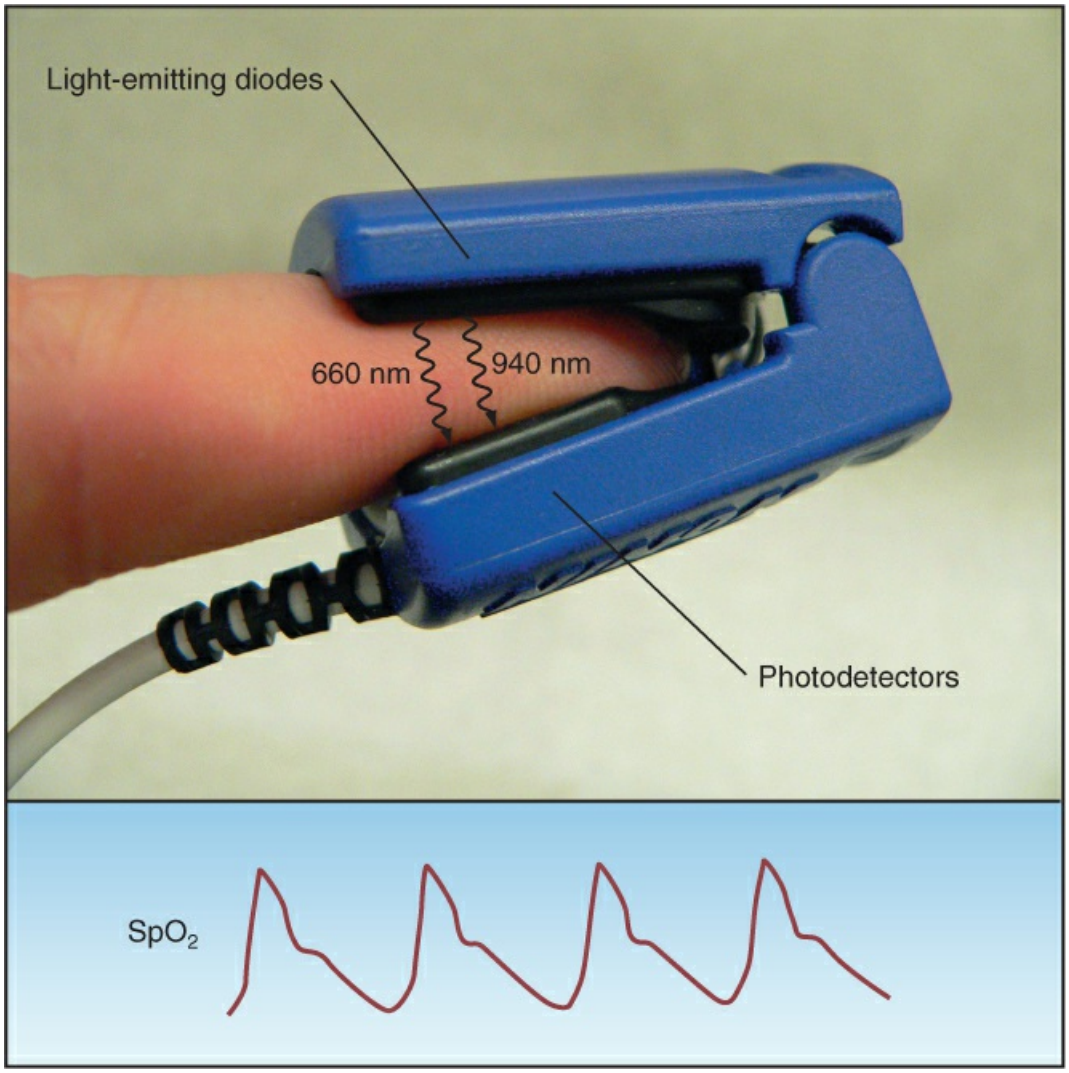

FIGURE 7.3 Pulse oximetry using a fingertip probe. The bottom panel shows the pulsatile photoplethysmography tracing. See text for explanation.

$$SpO_2 = (HbO_2 / Hb + HbO_2) \times 100 \quad (7.1)$$

Forehead Pulse Oximetry

The forehead is an appealing site for pulse oximetry because the arterial circulation in the forehead (which originates from the internal carotid artery) is less prone to vasoconstriction than the digital arteries in the fingers (5). Clinical studies have shown that pulse oximetry in the forehead can provide suitable SpO_2 measurements when fingertip SpO_2 recordings are compromised by hypotension or peripheral vasoconstriction (6).

Unlike fingertip oximetry, which is based on light *transmission*, forehead oximetry relies on light *reflectance*. This is illustrated in the right-sided panel in Figure 7.4. The forehead oximetry probe contains light-emitting diodes and photodetectors positioned next to each other, and the intensity of light reflected back from the underlying arteries is recorded and processed to derive the SpO_2. (*Note:* This is also the method used by smartwatches to monitor arterial oxygenation.)

THE ELASTIC HEADBAND: Venous pulsations can be prominent in the forehead region (especially during positive-pressure ventilation), and can be misread as arterial pulsations, resulting in spurious SpO_2 recordings. Elastic headbands have been shown to reduce the risk of interference from venous pulsations (7), and these headbands are used routinely with forehead pulse oximetry.

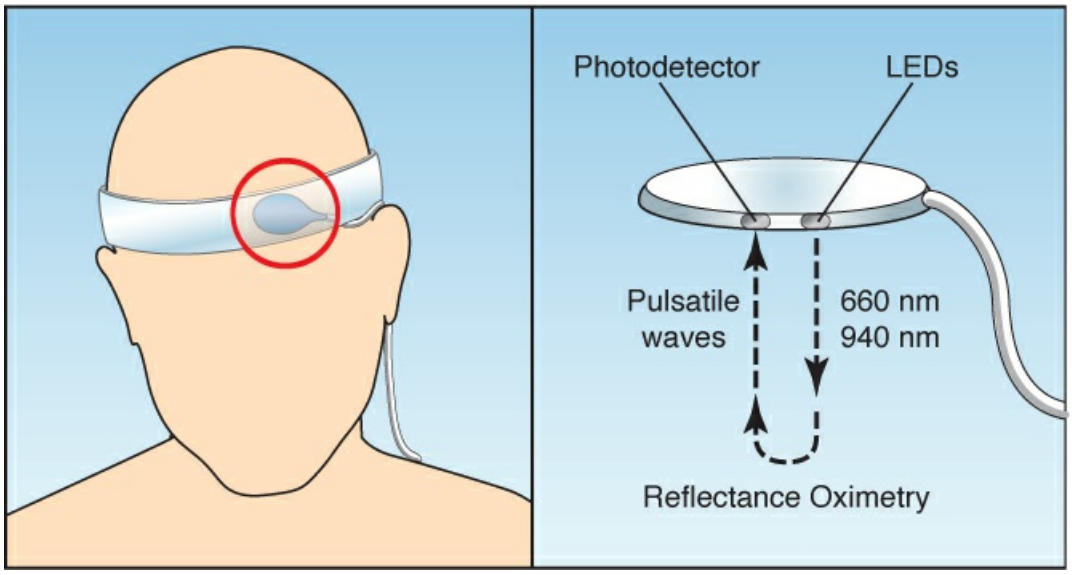

FIGURE 7.4 Forehead pulse oximetry., The forehead probe (circled in red) is placed just above the eyebrows, and is secured with an elastic headband to reduce venous pulsations. This method uses light reflectance to determine the SpO_2. See text for further explanation.

CO-Oximetry

Standard pulse oximeters do not detect carboxyhemoglobin (COHb) or methemoglobin (metHb) in blood. This requires additional wavelengths of light, and these are available in devices called "CO-oximeters" that generate up to 8 wavelengths of light to measure all forms of hemoglobin. These devices are located in clinical laboratories, and require an arterial blood sample. There is also a portable "pulse CO-oximeter" (Rainbow Pulse CO-oximeter, Masimo Corp, Irvine, CA) that has been used by firefighters and emergency personnel to detect carbon monoxide intoxication, but the accuracy of this device has been inconsistent (4).

Normally, metHb and COHb account for less than 5% of the total hemoglobin pool in blood (7,8). When these hemoglobin variants are abnormally elevated, the arterial O_2 saturation (SaO_2) decreases because HbO_2 is a lower fraction of the total hemoglobin pool. However, the SpO_2 from pulse oximetry is only marginally influenced by COHb or metHb levels (9–11). Therefore, *in cases of methemoglobinemia and carbon monoxide poisoning, the SpO_2 overestimates the actual SaO_2, and is not a reliable marker of arterial O_2 desaturation.* When abnormal elevations of metHb or COHb are suspected, an arterial blood sample should be sent to the hospital laboratory for a complete oximetry assessment. (Carbon monoxide poisoning and methemoglobinemia are described in Chapter 53.)

Accuracy

The accuracy of a single SpO_2 measurement is 3–4%, and the accuracy of serial measurements is 2–3% (4). The SpO_2 is usually higher than the arterial O_2 saturation (SaO_2), which may reflect the undetected decrease in SaO_2 from the small amounts of COHb and metHb in blood. The discrepancy between SpO_2 and SaO_2 is greater (by 1–3%) in subjects with dark skin pigmentation (12).

Undetected Hypoxemia

The tendency for the SpO_2 to overestimate the SaO_2 can result in instances of undetected hypoxemia, and these are more frequent in patients with dark skin pigmentation (8,9). In one study that included 88,000 paired measurements of SaO_2 and SpO_2, the incidence of undetected hypoxemia (i.e., SaO_2 <88% with SpO_2 ≥92%) was 6.9% in Blacks, 6.0% in Hispanics, and 4.9% in Whites and Asians. Since these discrepancies were recorded at one point in time, their clinical significance is unclear.

OXIMETRY: APPLICATIONS

Pulse oximetry is indicated in any situation where arterial oxygenation is a concern, and it is considered a requirement for patient safety in certain areas of the hospital (e.g., ICUs and operating suites). Therefore, the important issue concerning pulse oximetry in the ICU is not when to use it, but how to use it. The following information is relevant in this regard.

Arterial Oxygenation

As a surrogate measure of the arterial oxyhemoglobin saturation (SaO_2), the SpO_2 provides information about the oxygen concentration in arterial blood (CaO_2). The determinants of CaO_2 are identified in the following equation:

$$CaO_2 = 1.34 \times [Hb] \times SaO_2 \qquad (7.2)$$

where 1.34 is the oxygen binding capacity of hemoglobin (mL/g), [Hb] is the hemoglobin concentration (g/dL), and SaO_2 is expressed as a percentage, but in decimal notation (e.g., 0.75 instead of 75%). For a healthy adult with [Hb] = 15 g/dL and SaO_2 = 0.98, the CaO_2 is (1.34 × 15 x 0.98) = 19.7 mL/dL (or 197 mL/L).

Target SpO_2

The most recent clinical practice guideline for oxygen therapy recommends a target SpO_2 of 90–94% for most patients, and a slightly lower target (88–92%) for patients with hypercapnic respiratory failure (10). (For more on the target SpO_2 during oxygen therapy, see Chapter 25.) A change in SpO_2 of 3–4% is considered a significant change (4).

Venous Oximetry

Oximetry can also be used to measure the O_2 saturation in venous blood from the pulmonary artery (i.e., mixed venous blood) or the superior vena cava (i.e., central venous blood). This

measurement can be obtained by sending a blood sample (from either site) to the lab for CO-oximetry, but there are also specialized "oximetry catheters" that can continuously monitor the venous O_2 saturation in the superior vena cava or pulmonary artery. The operation of these catheters is illustrated in Figure 7.5. Oximetry catheters contain fiberoptic bundles that emit two wavelengths of light from the tip of the catheter (the same two wavelength used in pulse oximeters). Another channel of the catheter is connected to a photodetector that records the intensity of light that is reflected back from the hemoglobin in circulating erythrocytes. This technique (reflectance oximetry) is similar to the one used in forehead pulse oximetry. Oximetry catheters process and display the venous O_2 saturation every 5 seconds.

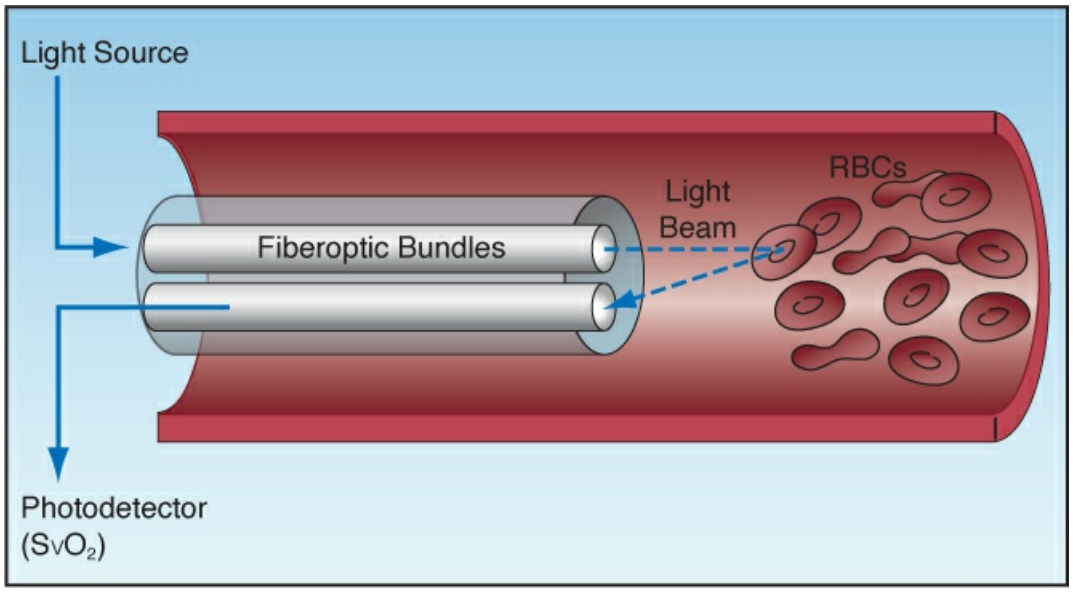

FIGURE 7.5 Continuous monitoring of venous O_2 saturation (SvO_2) using catheters capable of reflectance oximetry. See text for explanation.

Venous O_2 Saturation

The venous O_2 saturation (SvO_2) is a reflection of the balance between systemic O_2 delivery (DO_2) and O_2 consumption (VO_2), as described by the equation below:

$$SvO_2 = 1 - VO_2/DO_2 \qquad (7.3)$$

(For the derivation of this equation, see Chapter 9.) Thus, a decrease in SvO_2 from its normal value of 70 – 75% indicates a decrease in O_2 delivery relative to O_2 consumption.

Mixed Venous O_2 Saturation

The O_2 saturation in the pulmonary arteries (called the "mixed venous" O_2 saturation) is an "averaged" SvO_2 from all venous effluents (except the bronchial veins, which drain into the pulmonary veins). This measurement requires a pulmonary artery catheter (described in the next chapter), and there are specialized pulmonary artery oximetry catheters that continuously monitor the SvO_2 with an accuracy of 1–2% (13). Studies in ventilator-dependent patients

showed that the SvO_2 varies an average of 5–6% over just a few hours in patients who are clinically stable (14). Therefore as a general rule, a change in SvO_2 is considered significant if it exceeds 5% and persists for longer than 10 minutes (15).

Central Venous O_2 Saturation

The decreased popularity of the pulmonary artery catheter has shifted attention to the O_2 saturation in the superior vena cava, called the "central venous O_2 saturation" ($ScvO_2$), as a surrogate measure of the SvO_2. The $ScvO_2$ measured by central venous oximetry catheters is slightly lower than the SvO_2, but in patients with circulatory shock, the $ScvO_2$ is greater than the SvO_2 (16). (This change is attributed to the redistribution of blood flow to the cerebral circulation in circulatory shock.) Single measurements of $ScvO_2$ can differ from SvO_2 by as much as 10% in patients who are hemodynamically unstable, but the difference is reduced (to within 5%) when multiple measurements are obtained (17). Therefore, the $ScvO_2$ seems most valuable in identifying *trends* in the balance between DO_2 and VO_2.

Dual Oximetry

The interpretive value of SvO_2 (or $ScvO_2$) can be enhanced by adding the SpO_2 from pulse oximetry. The difference ($SpO_2 – SvO_2$) is roughly equivalent to the O_2 extraction from capillary blood (18), so the following relationships should hold:

$$VO_2 = DO_2 \times (SpO_2 – SvO_2) \tag{7.4}$$

(These relationships are described in detail in Chapter 9.) When O_2 delivery (DO_2) begins to decline (from a decrease in cardiac output, anemia, or hypoxemia), there is an increase in O_2 extraction from capillary blood ($SpO_2–SvO_2$), and this helps to maintain a constant O_2 consumption (VO_2). The ($SpO_2–SvO_2$) increases in a linear fashion from a normal value of about 0.25 (25%) up to a value of about 0.50 (50%). Beyond this, any further decrease in DO_2 elicits less of an increase in ($SpO_2–SvO_2$), and this marks the onset of oxygen-limited metabolism. Therefore, the following interpretations of the ($SpO_2– SvO_2$) are possible:

. An ($SpO_2–SvO_2$) >25% indicates that O_2 delivery is reduced (from low cardiac output, anemia, or hypoxemia) relative to O_2 consumption.

. An ($SpO_2–SvO_2$) >25% but <50% indicates that O_2 delivery is reduced, but not enough to compromise aerobic metabolism.

. An ($SpO_2– SvO_2$) ≥50% indicates a threat to aerobic metabolism.

The utility of ($SpO_2–SvO_2$) monitoring is demonstrated by a study showing that an ($SpO_2–SvO_2$) ≥50% is a valid indicator for the transfusion of packed red blood cells to correct anemia (19).

CAPNOGRAPHY: METHODOLOGY

The detection of CO_2 in exhaled gas can be done qualitatively (using colorimetric CO_2 detectors to verify entry into the trachea during endotracheal intubation) or quantitatively (using infrared capnography); this section will focus on the latter methodology and how it can be used.

Infrared Capnography

The quantitative method of monitoring exhaled CO_2 is based on the ability of CO_2 to absorb light in the infrared spectrum. The use of this method during mechanical ventilation is illustrated in Figure 7.6 (20,21). An infrared CO_2 probe is placed between the ventilator and the patient, and it emits a continuous infrared light beam that travels through the respired gas (22). On the opposite side of the probe is a rapid-response photodetector that records the intensity of infrared light transmission and processes the information to generate a display of the changes in PCO_2 that occur during each exhalation. This is called a *capnogram*.

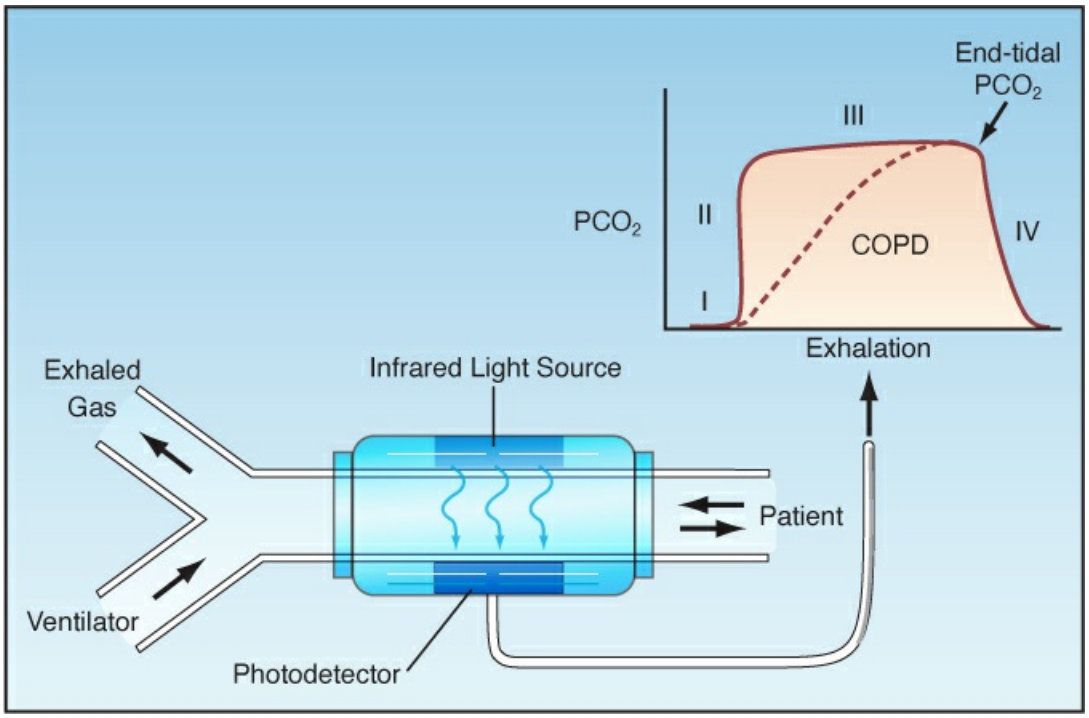

FIGURE 7.6 Infrared capnography during mechanical ventilation. The CO_2 probe sits between the ventilator and the patient, and transmits a continuous infrared light beam through the respired gas. The photodetector processes the transmitted light and generates a record of the changes in PCO_2 that occur during each exhalation (the capnogram). See text for further explanation.

The Capnogram

As shown in Figure 7.6, the capnogram is separated into four phases. Phase I represents the very start of expiration, where the expired gas is from the anatomic dead space, and has negligible amounts of CO_2. In phase II, the exhaled CO_2 steadily rises, and the rate of rise is rapid when alveolar ventilation is well matched to perfusion (i.e., in the normal lung). A slowly rising phase II indicates an increase in alveolar dead space (since these alveoli have a low PCO_2), which occurs in COPD. Phase III is normally a plateau, indicating that alveolar emptying has reached a

steady state, and Phase IV is the onset of inhalation.

Nonintubated Patients

End-tidal CO_2 monitoring is also available for spontaneously breathing (non-intubated) patients using infrared CO_2 probes that are specially designed for nasal cannulas and facemasks. An example of a CO_2 detection system for nasal cannulas is illustrated in Figure 7.7. In this case, a miniaturized infrared CO_2 probe (like the one in Figure 7.6) is placed in-line with a nasal cannula and an adapter that collects orally exhaled gas. Oxygen is delivered through another cannula in the system.

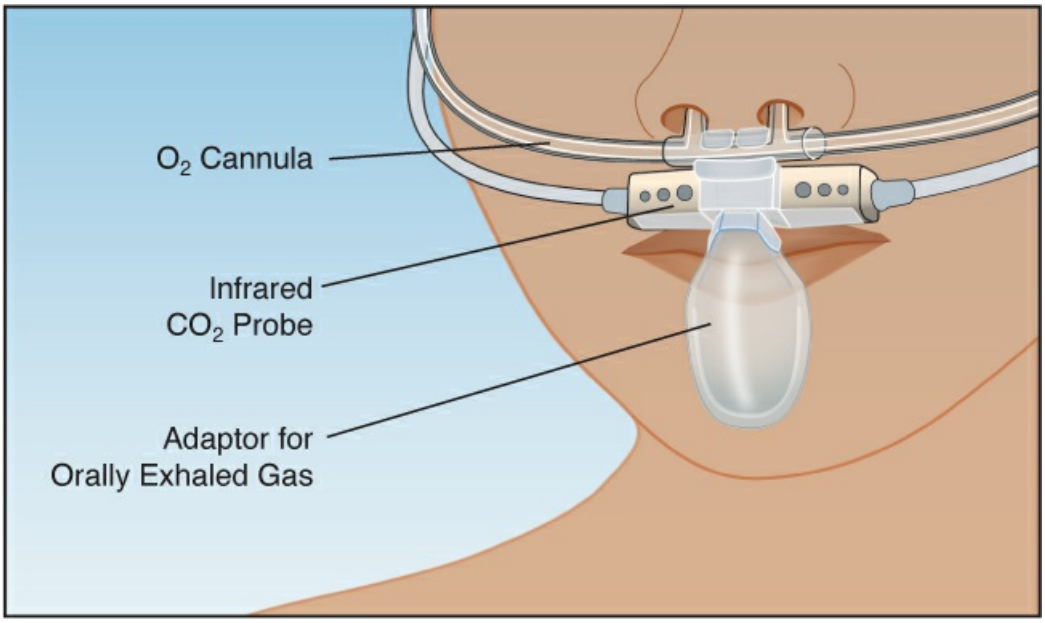

FIGURE 7.7 A modified infrared CO_2 probe (capONE, Nihon Kohden, Tokyo, Japan) for monitoring end-tidal PCO_2 during spontaneous breathing.

CAPNOGRAPHY: APPLICATIONS

Procedures

Procedural Sedation

The sedation used for a variety of procedures creates a risk of hypoventilation, especially in patients with any of the following conditions: advanced age, obesity, sleep apnea, or chronic CO_2 retention from obstructive lung disease. Hypoventilation causes an increase in end-tidal PCO_2 ($P_{ET}CO_2$), and this change occurs before the decrease in SpO_2. Capnography has proven superior to oximetry for detecting hypoventilation during procedural sedation (20,23); as a result, monitoring $P_{ET}CO_2$ is recommended in all instances where procedural sedation is used (24).

Endotracheal Intubation

For placement of endotracheal tubes, verification of tracheal placement with exhaled CO_2 detection (either with colorimetric or infrared CO_2 detectors) has become a "standard of care" (25) for the following reasons:

. Unrecognized esophageal intubation (which can be fatal) is reported in one of every 18 emergency intubations in critically ill patients (26).

. Clinical assessment, such as auscultation for breath sounds, does not always differentiate between tracheal and esophageal intubation (27).

There are also situations where exhaled CO_2 is negligible despite tracheal placement of an endotracheal tube. This occurs primarily during cardiac arrest, when there is little or no venous return to deliver CO_2 to the alveoli. Severe bronchospasm has also been proposed as a cause of this condition, but this has not been adequately verified (24).

Changes in Cardiac Output

One of the most promising applications of end-tidal PCO_2 monitoring is the detection of acute changes in cardiac output. The correlation between changes in $P_{ET}CO_2$ and changes in cardiac output is demonstrated in Figure 7.8 (28). This relationship suggests that $P_{ET}CO_2$ monitoring might be valuable for detecting cardiac output responses to interventions such as volume loading. In this context, the available studies have shown that changes in $P_{ET}CO_2$ are predictive of fluid responsiveness in mechanically ventilated patients (29), but not in spontaneously breathing healthy patients (30). This application deserves further attention.

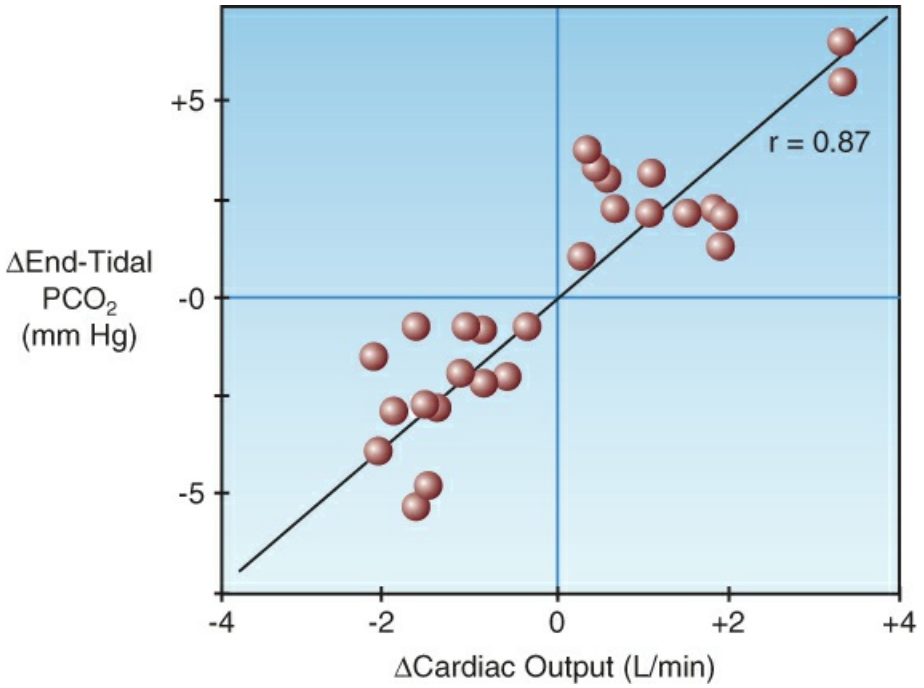

FIGURE 7.8 Relationship between changes in end tidal PCO_2 and changes in cardiac output in a group of postoperative patients. r = correlation coefficient. Data from Reference 28. See text for further explanation.

Cardiopulmonary Resuscitation

One successful application of the relationship between $P_{ET}CO_2$ and cardiac output has been the predictive value of end-tidal CO_2 monitoring during cardiopulmonary resuscitation; i.e., studies indicate that return of spontaneous circulation is unlikely if the $P_{ET}CO_2$ is ≤10 mm Hg after 20 minutes of cardiopulmonary resuscitation (31). This topic is presented in detail in Chapter 21.

$PaCO_2$ – $P_{ET}CO_2$ Difference

Although the $P_{ET}CO_2$ is roughly equivalent to the $PaCO_2$ in healthy subjects, the $P_{ET}CO_2$ will decrease relative to the $PaCO_2$ in any condition associated with an increase in "dead space" ventilation (i.e., when alveoli are overventilated relative to perfusion). Most causes of respiratory failure are accompanied by an increase in physiologic dead space (see the left column in Table 7.1), and the magnitude of the

TABLE 7.1 Conditions that Alter the Relationship Between Arterial and End-Tidal PCO_2

$PETCO_2 < PaCO_2$	$PETCO_2 > PaCO_2$
• Leaky Ventilator Circuit • Excessive Lung Inflation • Pneumonia • Obstructive Lung Disease • Pulmonary Edema • Pulmonary Embolism • Acute Decrease in Cardiac Output	• Hypermetabolism • Metabolic Acidosis • Hyperoxia

($PaCO_2$ - $P_{ET}CO_2$) difference can be used to follow the clinical course of the underlying disorder (21). During mechanical ventilation, an increase in the ($PaCO_2$ - $P_{ET}CO_2$) difference can be partly due to overventilation (e.g., from excessive inflation volumes), so the $PaCO_2$ - $P_{ET}CO_2$ difference can help to identify the optimal inflation volume during mechanical ventilation.

A FINAL WORD

Helping Fill the Void

The fall from grace of the pulmonary artery catheter has created a void in the ability to evaluate tissue perfusion and oxygenation, but oximetry and capnography can help to fill this void in the following ways:

. Monitoring the SpO_2 with pulse oximetry provides no information about tissue oxygenation, but the use of "dual oximetry" to monitor the ($SpO–SvO_2$) difference provides information about the threat of inadequate tissue oxygenation.

. Monitoring the end-tidal PCO_2 ($P_{ET}CO_2$) can be useful for detecting acute changes in cardiac

output, and it is particularly valuable as a prognostic aid in cardiopulmonary resuscitation.

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Chapter 8

The Pulmonary Artery Catheter

A searchlight cannot be used effectively without a fairly thorough knowledge of the territory to be searched.

Fergus Macartney (*a*)

In 1970, a vascular catheter was introduced that would revolutionize the practice of bedside hemodynamic monitoring (1). It was a very long, centrally-placed catheter with a small inflatable balloon at its distal end. When inflated, the balloon allowed the flow of venous blood to carry the catheter through the right side of the heart and into one of the pulmonary arteries (like floating down a river on an inflatable inner tube). This balloon flotation effect allowed a right heart catheterization to be performed at the bedside, without the need for fluoroscopic guidance. An added bonus was a temperature-sensitive thermistor on the catheter, which allowed measurements of cardiac output using the *thermodilution* technique. When used appropriately, this *pulmonary artery balloon flotation catheter* could generate a comprehensive set of physiological measurements for evaluating cardiac performance and systemic oxygen transport (2).

Not surprisingly, the pulmonary artery (PA) catheter gained rapid and widespread acceptance, and became a staple of critical care management in the latter years of the twentieth century. However, storm clouds appeared in the early years of the twenty-first century, when a series of (poorly designed) clinical studies showed that PA catheters did not improve survival (3). The fallout from these studies was a swift and precipitous decline in the use of PA catheters; e.g., one large survey showed a 70% decrease in PA catheter use over the years from 1999 to 2013 (4).

The PA catheter's fall from grace is undeserved (see A FINAL WORD at the end of the chapter), as this catheter provides a wealth of information that can be useful if applied appropriately (5,6). The goal of this chapter is to introduce you to these measurements, and how they are obtained. As suggested in the introductory quote, the benefit derived from the PA catheter will depend on your knowledge of cardiovascular physiology.

THE CATHETER

The basic features of a PA catheter are shown in Figure 8.1. The catheter is 110 cm long and has an outside diameter of 2.3 mm (about 7 French). There are two internal channels: one channel emerges at the tip of the catheter (the distal or PA lumen), and the other channel emerges 30 cm proximal to the catheter tip (the proximal or RA lumen), which should be situated in the right atrium. The tip of the catheter has a small inflatable balloon (1.5 mL capacity) that helps to carry the catheter to its final destination. When the balloon is fully inflated, it creates a recess for the tip of the catheter that prevents the tip from scraping along the vessel wall as the catheter is advanced. A small thermistor (a temperature-sensing transducer) is placed near the tip of the catheter, and is used to measure the cardiac output using the thermodilution technique (described later in the chapter).

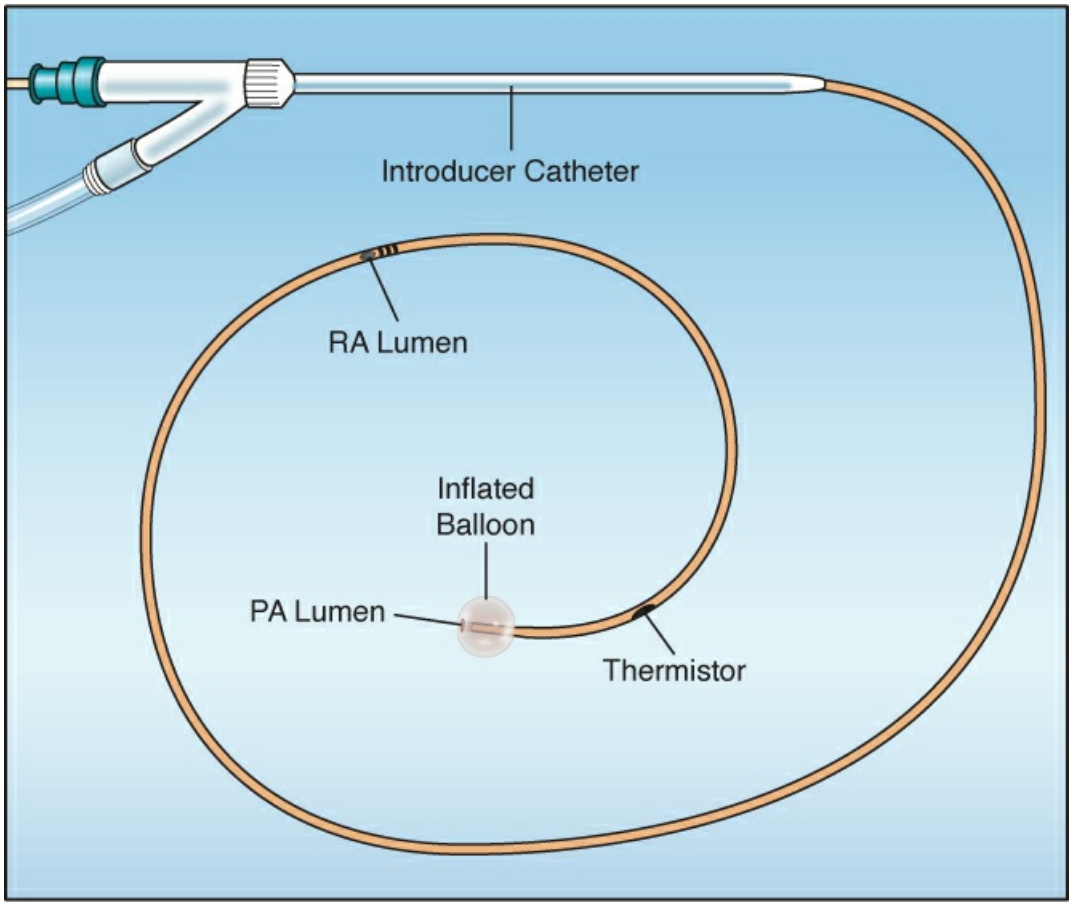

FIGURE 8.1 The basic features of a pulmonary artery (PA) catheter. Note that the PA catheter has been threaded through a large-bore introducer catheter that has a side-arm infusion port.

Catheter Placement

The PA catheter is inserted through a large bore (8–9 French) introducer sheath that has been placed in the subclavian vein or internal jugular vein (see Figure 8.1). The distal lumen of the catheter is attached to a pressure transducer to monitor vascular pressures as the catheter is advanced. When the catheter is passed through the introducer sheath and enters the superior vena cava, a venous pressure waveform appears. When this occurs, the balloon is inflated with 1.5 mL of air, and the catheter is advanced with the balloon inflated. The location of the catheter tip is

determined by the pressure tracings recorded from the distal lumen, as shown in Figure 8.2.

. The superior vena cava pressure is identified by a venous pressure waveform, which appears as small amplitude oscillations. This pressure remains unchanged until the catheter enters the right ventricle, and it represents the mean pressure in the right atrium, more commonly known as the *central venous pressure*.

. When the catheter tip is advanced across the tricuspid valve and into the right ventricle, a pulsatile waveform appears. The peak (systolic) pressure is a function of the strength of right ventricular contraction, and the lowest (diastolic) pressure is equivalent to the mean right atrial pressure.

. When the catheter moves across the pulmonic valve and into a main pulmonary artery, the pressure waveform shows a sudden rise in diastolic pressure with no change in the systolic pressure. (*Note:* The systolic pressure will increase in the presence of pulmonary hypertension). The rise in diastolic pressure is caused by resistance to flow in the pulmonary circulation.

. As the catheter is advanced along the pulmonary artery, the pulsatile waveform disappears, leaving a nonpulsatile pressure that is normally at the same level as the diastolic pressure of the pulsatile waveform. This is the *pulmonary artery occlusion pressure*, more commonly known as the *wedge pressure*, and is a reflection of the filling pressure on the left side of the heart (see the next section).

. When the wedge pressure tracing appears, the balloon is deflated, and the pulsatile pressure waveform should reappear. The catheter is then secured in place, and the balloon is left deflated. (*Note:* Prolonged balloon inflation creates the risk of pulmonary artery rupture or pulmonary infarction.)

. On occasion, the pulsatile pressure in the pulmonary arteries never disappears despite advancing the catheter maximally. In this situation, the pulmonary artery diastolic pressure can be used as a surrogate measure of the wedge pressure, but only if there is no evidence of pulmonary hypertension (see next section).

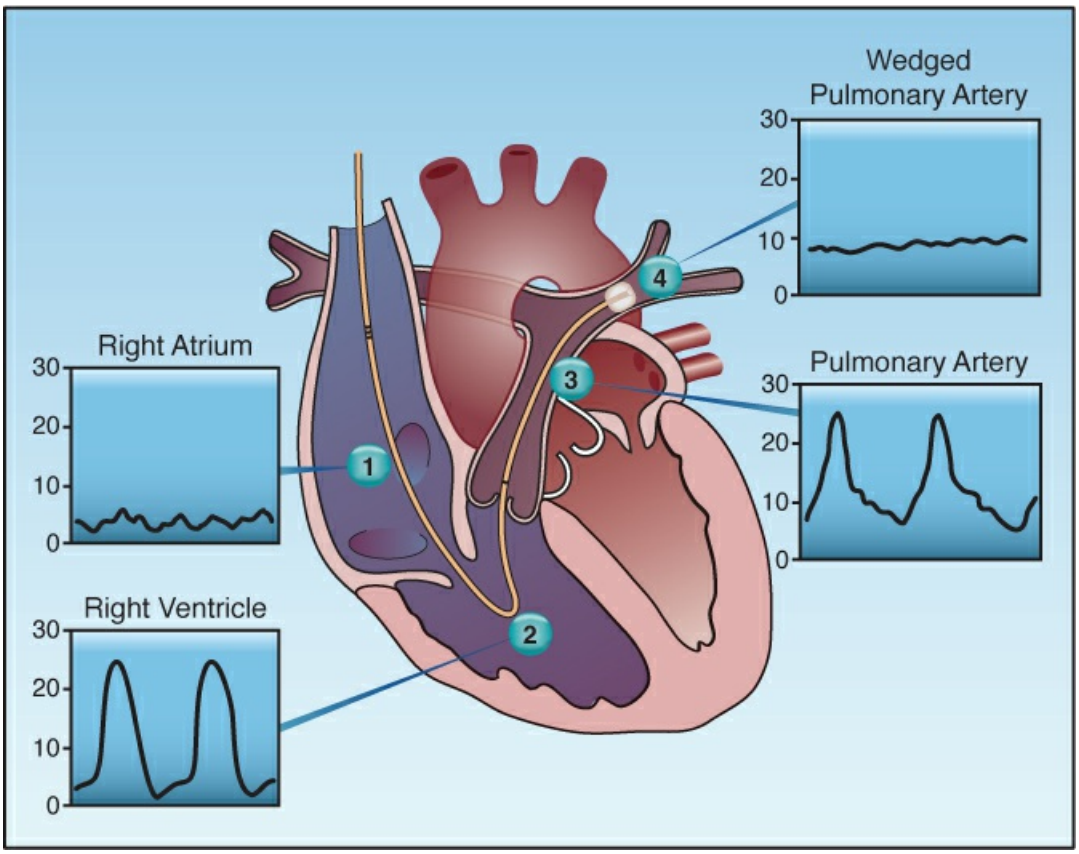

FIGURE 8.2 The pressure waveforms at different points along the normal course of a pulmonary artery catheter. These waveforms are used to identify the location of the catheter tip as it is advanced.

THE WEDGE PRESSURE

The wedge pressure is obtained by slowly inflating the balloon at the tip of the PA catheter until the pulsatile pressure disappears, as shown in Figure 8.3. Note that the wedge pressure is at the same level as the diastolic pressure in the pulmonary artery. This relationship is altered in pulmonary hypertension, where the wedge pressure is lower than the pulmonary artery diastolic pressure.

Wedge Pressure Tracing

The wedge pressure represents the venous pressure on the left side of the heart, and the magnified section of the wedge pressure in Figure 8.3 shows a contour that is similar to the venous pressure on the right side of the heart. The *a* wave is produced by left atrial contraction, the *c* wave is produced by closure of the mitral valve (during isometric contraction of the left ventricle), and the *v* wave is produced by systolic contraction of the left ventricle against a closed mitral valve. These components are often difficult to distinguish, but prominent *v* waves are readily apparent in patients with mitral regurgitation.

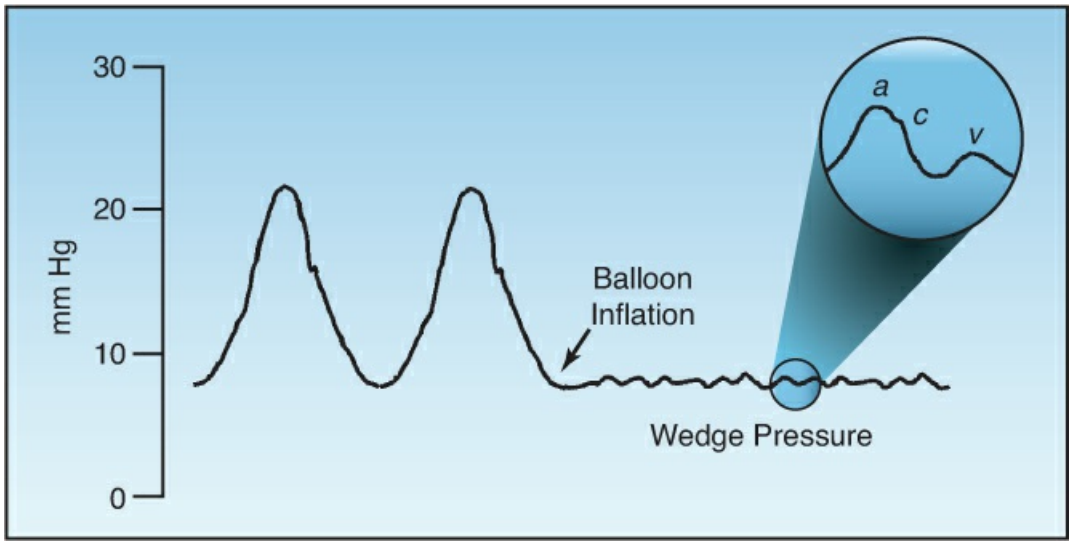

FIGURE 8.3 Pressure tracing showing the transition from a pulsatile pulmonary artery pressure to a balloon occlusion (wedge) pressure. The magnified area shows the components of the wedge pressure: *a* wave (atrial contraction), *c* wave (mitral valve closure), and *v* wave (ventricular contraction).

Wedge Pressure Principle

The underlying principle for the wedge pressure is illustrated in Figure 8.4. When the balloon on the PA catheter is inflated to obstruct flow (Q = 0), there is a static column of blood between the tip of the catheter and the left atrium, and the wedge pressure at the tip of the catheter (P_W) is equivalent to the pulmonary capillary pressure (P_C) and the pressure in the left atrium (P_{LA}). To summarize: if Q = 0, then $P_W = P_C = P_{LA}$. If the mitral valve is behaving normally, the wedge pressure (left atrial pressure) will be equivalent to the left ventricular end-diastolic pressure. Therefore, *in the absence of mitral valve disease, the wedge pressure is a measure of the filling pressure of the left ventricle*.

Respiratory Variations

The wedge pressure is a reflection of the left atrial pressure only if the pulmonary capillary pressure is greater than the alveolar pressure ($P_C > P_A$ in Figure 8.4), otherwise the wedge pressure will reflect the alveolar pressure. This latter condition occurs when there are respiratory variations in the wedge pressure tracing (7). When this occurs, the wedge pressure should be measured at the end of expiration, as explained next.

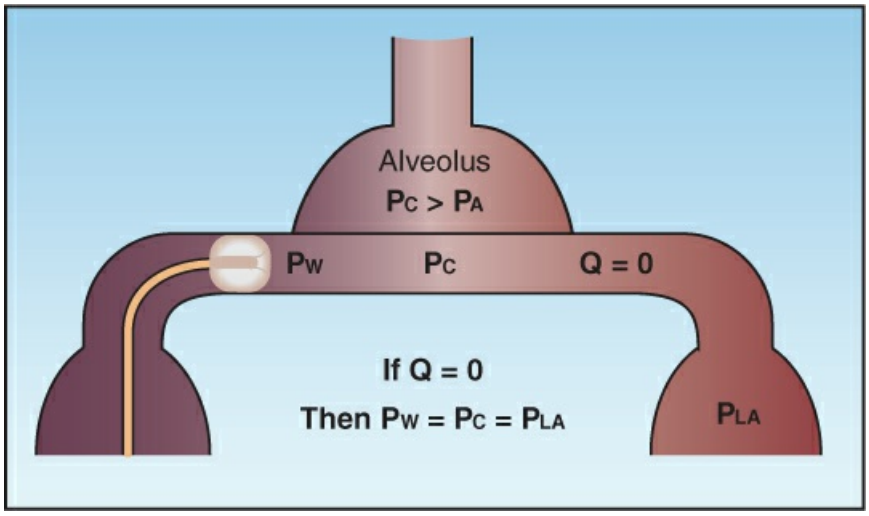

FIGURE 8.4 The basis of the wedge pressure measurement. When flow ceases because of balloon inflation (Q = 0), the wedge pressure (PW) is equivalent to the pulmonary capillary pressure (PC) and the pressure in the left atrium (PLA). This occurs only when the pulmonary capillary pressure is greater than the alveolar pressure (PC > PA).

Changes in intrathoracic pressure can be transmitted into intrathoracic blood vessels (usually low pressure vessels like veins and capillaries), and this creates respiratory variations in the recorded pressure. This is illustrated in Figure 8.5 for a central venous pressure (CVP) tracing. The undulating pattern in the recorded (intravascular) pressure is misleading, because the physiologically important (transmural) pressure is not changing. When this occurs, *the pressure should be measured at the end of expiration, when the intrathoracic pressure is zero (i.e., atmospheric pressure) and the intravascular and transmural pressures are equivalent*. The pressure tracing in Figure 8.5 was recorded during positive pressure mechanical ventilation, so the end-expiratory pressure is the lowest point in each of the pressure undulations. (If this tracing was obtained during spontaneous breathing, the end-expiratory pressure would be the peak pressure for each respiratory cycle.)

POSITIVE END-EXPIRATORY PRESSURE: Positive end-expiratory pressure (PEEP) can falsely elevate the wedge pressure (and CVP) at end-expiration because the intrathoracic pressure is higher than atmospheric (zero) pressure. When PEEP is applied during mechanical ventilation (which is a routine practice), the patient can be briefly disconnected from the ventilator to measure the wedge pressure (8). For patients with ”intrinsic PEEP” (caused by incomplete emptying of the lungs), accurate measurements of the wedge pressure can be difficult (9). Chapter 29 includes a description of intrinsic PEEP and a method for correcting the wedge pressure in the presence of intrinsic PEEP.

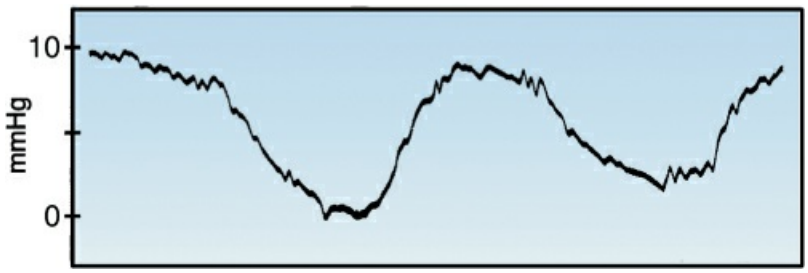

FIGURE 8.5 Respiratory variation in the central venous pressure (CVP) during mechanical ventilation. The CVP should be measured at the end of expiration, which corresponds to the lowest points in the pressure undulations. See text for further explanation.

Spontaneous Variations

In addition to respiratory variations, the wedge pressures can vary spontaneously. This variation in wedge pressure is ≤4 mm Hg in 60% of patients, but it can be as high as 7 mm Hg (10). In general, *a change in the wedge pressure of >4 mm Hg is considered a clinically significant change*.

Wedge vs Hydrostatic Pressure

The wedge pressure is often mistaken as the hydrostatic pressure in the pulmonary capillaries. However, this is not the case (11,12), because the wedge pressure is measured in the absence of blood flow. When the balloon is deflated and flow resumes, the pressure in the pulmonary capillaries (P_C) will be higher than the pressure in the left atrium (P_{LA}), and the difference in pressures will dependent on the flow rate (Q) and the resistance to flow in the pulmonary veins (RV); i.e.,

$$P_C - P_{LA} = Q \times RV \tag{8.1}$$

Since the wedge pressure (P_W) is equivalent to left atrial pressure (P_{LA}), Equation (8.1) can be restated as:

$$P_C - P_W = Q \times RV \tag{8.2}$$

Therefore, the capillary hydrostatic pressure must be greater than the wedge pressure to create a pressure gradient for venous flow to the left side of the heart. The magnitude of this difference is unclear because it is not possible to determine the resistance to flow in the pulmonary veins (RV). However, the $P_C - P_W$ difference will be magnified by conditions that promote pulmonary venoconstriction, such as hypoxemia, endotoxemia, vasopressor infusions, and the acute respiratory distress syndrome (13,14).

Wedge Pressure in ARDS

The wedge pressure has been used to differentiate hydrostatic (cardiogenic) pulmonary edema from the leaky-capillary pulmonary edema that characterizes the acute respiratory distress syndrome (ARDS); i.e., a normal wedge pressure is considered evidence of ARDS (15). However, since the capillary hydrostatic pressure is normally higher than the wedge pressure, and this difference is magnified in ARDS (14), *a normal wedge pressure does not exclude the*

diagnosis of hydrostatic pulmonary edema. Therefore, the use of a normal wedge pressure as a diagnostic criterion for ARDS should be abandoned.

THERMODILUTION CARDIAC OUTPUT

The presence of a temperature-sensitive thermistor on the PA catheter allows a measurement of the cardiac output by the thermodilution technique. This is considered the gold standard method for measuring cardiac output at the bedside.

The Method

The indicator dilution method of measuring blood flow is based on the premise that, when an indicator substance is added to circulating blood, the rate of blood flow is inversely proportional to the change in concentration of the indicator over time. The thermodilution method employs temperature as the indicator.

The thermodilution method is illustrated in Figure 8.6. A bolus (usually 10 mL) of a saline solution that is colder than blood is injected through the proximal port of the catheter in the right atrium. The cold fluid mixes with blood in the right heart chambers, and the cooled blood is ejected into the pulmonary artery and flows past the thermistor on the distal end of the catheter. The thermistor records the change in blood temperature with time. The area under this curve is inversely proportional to flow rate in the pulmonary artery, which is equivalent to the cardiac output (in the absence of intracardiac shunts). Electronic PA monitors integrate the area under the temperature–time curves and provide a digital display of the cardiac output.

Thermodilution Curves

Examples of thermodilution curves are shown in Figure 8.7. The low cardiac output curve (upper panel) has a gradual rise and fall, whereas the high output curve (middle panel) has a rapid rise, an abbreviated peak, and a steep downslope. Note that the area under the low cardiac output curve is greater than the area under the high output curve (i.e., indicating that the area under these curves is inversely related to the flow rate).

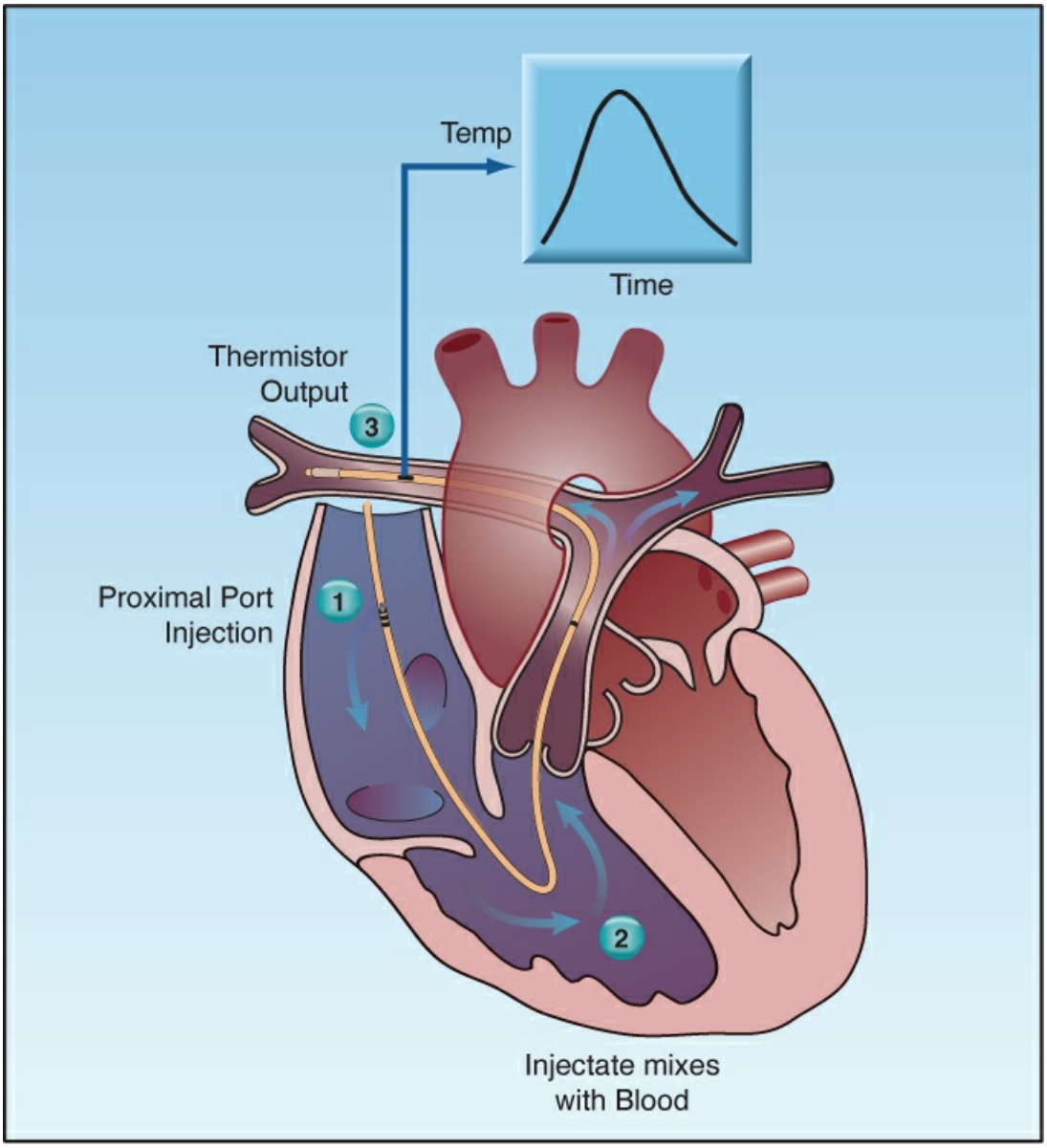

FIGURE 8.6 The thermodilution method of measuring cardiac output. See text for explanation.

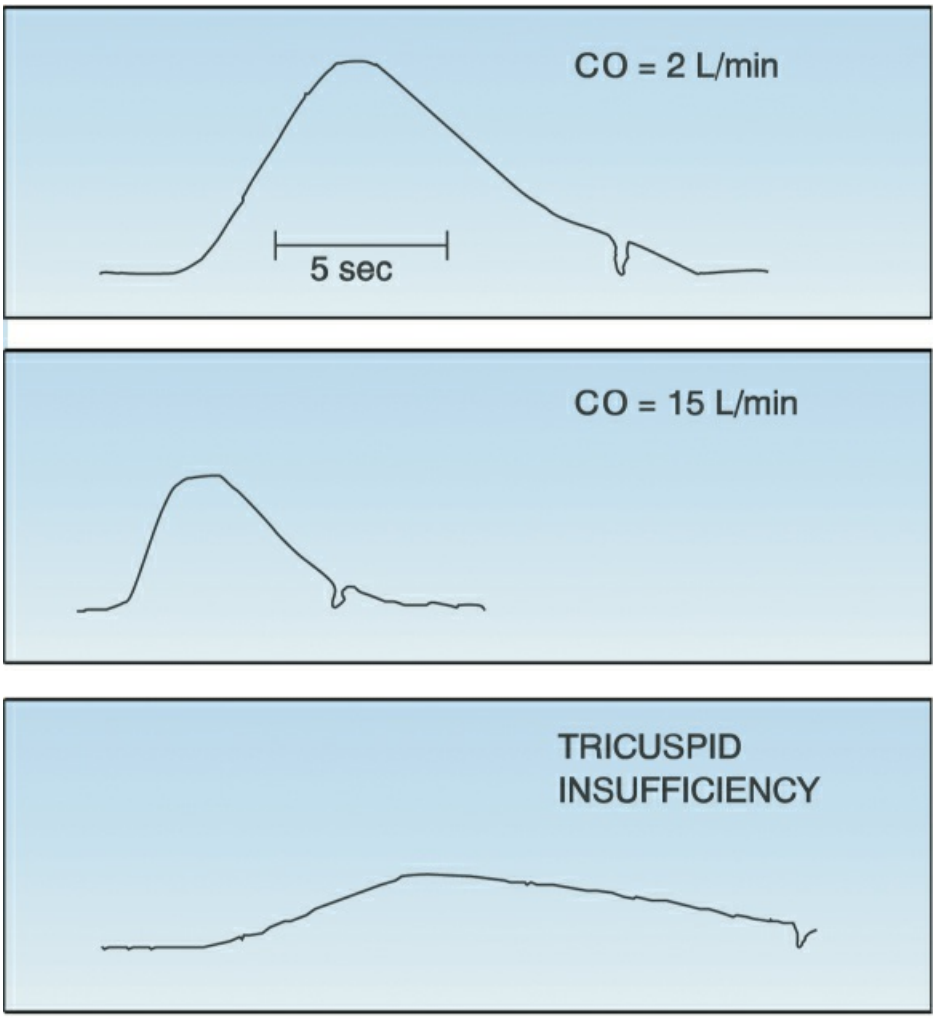

FIGURE 8.7 Thermodilution curves for a low cardiac output (upper panel), a high cardiac output (middle panel), and tricuspid insufficiency (lower panel). The sharp inflection in each curve marks the end of the measurement period. CO = cardiac output.

How Many Measurements?

Serial measurements are recommended for each cardiac output determination. Three measurements are sufficient if they differ by 10% or less, and the cardiac output is taken as the average of all measurements. Serial measurements that differ by more than 10% are considered unreliable (16).

Variability

Thermodilution cardiac output can vary by as much as 10% without any apparent change in the clinical condition of the patient (17). Therefore, *a change in thermodilution cardiac output should exceed 10% to be considered clinically significant.*

Sources of Error

As mentioned earlier, thermodilution is considered the gold standard method for measuring cardiac output at the bedside. However there are sources of error in the methodology, and the

more notable ones are summarized here.

Operator Error

Low-volume or inappropriately warm injectates can result in overestimation of the cardiac output, and variability in the timing of the injectate in relation to the respiratory cycle can also produce spurious results (6).

Tricuspid Regurgitation

Tricuspid regurgitation can result in underestimation or overestimation of the cardiac output (6). Regurgitant flow across the tricuspid valve causes the injectate to be recycled, producing a prolonged, low amplitude thermodilution curve similar to the one in the bottom frame of Figure 8.7. This results in a falsely low cardiac output measurement (18). Overestimation of the cardiac output can occur when the injectate is warmed because of recycling across the tricuspid valve.

Intracardiac Shunts

Intracardiac shunts produce falsely elevated cardiac output measurements. In right-to-left shunts, a portion of the cold indicator fluid passes through the shunt, thereby creating an abbreviated thermodilution curve similar to the high-output curve in the middle panel of Figure 8.7. In left-to-right shunts, the thermodilution curve is abbreviated because the shunted blood increases the blood volume in the right heart chambers, and this dilutes the indicator solution that is injected.

Continuous Cardiac Output Measurements

Pulmonary artery catheters are available that can provide thermodilution cardiac output measurements as rapidly as every 20 seconds, without the need for bolus injections of cold fluid. These catheters have a small heating filament (near the proximal port of the catheter) that is activated by brief, randomly-generated electrical pulses that raise the surrounding blood temperature by about 0.02°C. The downstream thermistor averages the temperature-time curves over a 3 minute period to determine the cardiac output, which is updated every 20–30 seconds. (The small temperature change creates a poor signal-to-noise ratio, which is why multiple temperature-time curves must be measured and averaged.) This “pulsed warm thermodilution technique” has shown a good correlation with the traditional “intermittent bolus” technique (19,20).

The automated continuous thermodilution technique provides a more dynamic assessment of the cardiac output, and it also eliminates the time commitment, risk of operator error, and the volume infusions associated with the intermittent bolus technique. Moreover, there are PA catheters that allow continuous monitoring of both cardiac output and mixed venous O_2 saturation (SvO_2) (21), which adds the ability to monitor an indirect measure of tissue oxygenation. (See Chapter 9 for an explanation of the SvO_2.)

CATHETER-DERIVED HEMODYNAMICS

The PA catheter provides a wealth of information on cardiovascular function and systemic oxygen transport The following is a description of 10 hemodynamic parameters that can be

monitored using PA catheters. These are listed in Table 8.1.

Body Size

Hemodynamic parameters are often expressed in relation to body size, and the favored measure of body size for hemodynamic measurements is the body surface area (BSA), which can be determined with the following simple equation (22):

$$\text{BSA } (m^2) = \text{Ht (cm)} + \text{Wt (kg)} - 60/100 \quad (8.3)$$

(*Note:* BSA is preferred over weight as an index of body size because cardiac output is linked to metabolic rate, and the basal metabolic rate is expressed in terms of body surface area.) Measurements that are expressed in relation to BSA are referred to as an "index" (e.g., cardiac index instead of cardiac output). The average-sized adult has a body surface area of 1.7 m^2.

TABLE 8.1 Measurements Available with PA Catheters

Parameter	Abbreviation	Normal Range
Central Venous Pressure	CVP	0–5 mm Hg
Pulmonary Artery Wedge Pressure	PAWP	6–12 mm Hg
Cardiac Index	CI	2.4–4.0 L/min/m^2
Stroke Index	SI	20–40 mL/m^2
Systemic Vascular Resistance Index	SVRI	25–30 Wood Units†
Pulmonary Vascular Resistance Index	PVRI	1–2 Wood Units†
Mixed Venous O_2	SvO_2	70–75%
Oxygen Delivery (Index)	DO_2	520–570 mL/min/m^2
Oxygen Uptake (Index)	VO_2	110–160 mL/min/m^2
Oxygen Extraction Ratio	O_2ER	0.2–0.3

†mm Hg /L/min/m^2.

Cardiovascular Parameters

The following parameters are used to evaluate cardiac performance and global tissue perfusion. The reference ranges for these parameters are included in Table 8.1 Size-adjusted parameters are expressed as an *index* (e.g., cardiac index instead of cardiac output).

Central Venous Pressure

When the PA catheter is properly placed, the proximal port of the catheter will be in the right atrium, and the pressure recorded from this port should be the right atrial pressure (PRA). As mentioned previously, the pressure in the right atrium is the same as the pressure in the superior vena cava, and these pressures are collectively called the central venous pressure (CVP). In the absence of tricuspid valve dysfunction, the CVP should be equivalent to the right ventricular end diastolic pressure (RVEDP).

$$CVP = P_{RA} = RVEDP \tag{8.4}$$

The CVP is then a measure of the filling pressure for the right side of the heart. The normal range for the CVP is 0–5 mm Hg, and it can be a negative pressure in the sitting position.

Wedge Pressure

As described earlier, the pulmonary artery wedge pressure (PAWP) is a measure of the left atrial pressure (P_{LA}), and this pressure should be equivalent to the left ventricular end diastolic pressure (LVEDP) when mitral valve function is normal.

$$PAWP = P_{LA} = LVEDP \tag{8.5}$$

The wedge pressure is thus a measure of the filling pressure for the left side of the heart. This pressure is slightly higher than the CVP (to keep the foramen ovale closed), and the normal range is 6–12 mm Hg.

Cardiac Index

The cardiac output (CO) measurement is the single most important contribution of the PA catheter to hemodynamic assessments, as it not only provides an assessment of cardiac contractile strength (using the stroke volume), it also creates the ability to monitor systemic oxygen transport (see later). The cardiac output is typically expressed in relation to body surface area (BSA), and is called the *cardiac index* (CI).

$$CI = CO/BSA \tag{8.6}$$

The normal range for the cardiac index is 2.4–4 L/min/m^2, which is typically about 60% of the normal range for the cardiac output.

Stroke Index

The stroke volume (i.e., the volume of blood ejected during systole) is used to assess the strength of ventricular contractions, and the relationship between stroke volume and the pulmonary artery wedge pressure can be used to generate ventricular function curves. When adjusted for body size, the stroke volume is called the *stroke index* (SI), and it is derived as the cardiac index (CI) divided by the heart rate (HR):

$$SI = CI/HR \tag{8.7}$$

The normal range of the SI in adults is 20–40 mL/m^2.

Systemic Vascular Resistance Index

The hydraulic resistance in the systemic circulation is not a measurable quantity for a variety of reasons (e.g., resistance is flow-dependent and varies in different regions). Instead, the systemic vascular resistance (SVR) is a global measure of the relationship between systemic pressure and flow. The SVR is directly related to the mean pressure drop from the aorta to the right atrium (i.e., mean arterial pressure or MAP minus the CVP), and is inversely related to the cardiac

output. The size-adjusted SVR index (SVRI) is derived using the cardiac index (CI).

$$SVRI = (MAP - CVP)/CI \tag{8.8}$$

The SVRI is expressed in Wood units (mm Hg/L/min/m^2), which can be multiplied by 80 to obtain more conventional units of resistance (dynes·sec^{-1}·cm^{-5}/m^2), but this conversion offers no advantage (23).

Pulmonary Vascular Resistance Index

The pulmonary vascular resistance (PVR) has the same limitations as mentioned for the systemic vascular resistance. The PVR is a global measure of the relationship between pressure and flow in the lungs, and is derived as the mean pressure drop from the pulmonary artery to the left atrium, divided by the cardiac output. Because the pulmonary artery wedge pressure (PAWP) is equivalent to the left atrial pressure, the pressure gradient across the lungs can be expressed as the difference between the mean pulmonary artery pressure and the wedge pressure (PAP – PAWP). The size-adjusted PVR index (PVRI) is derived using the cardiac index (CI):

$$PVRI = (PAP - PAWP)/CI \tag{8.9}$$

Like the SVRI, the PVRI is expressed in Wood units (mm Hg/L/min/m^2).

Oxygen Transport Parameters

The oxygen transport parameters provide a global measure of oxygen supply and oxygen consumption. These parameters are described in detail in Chapter 9.

Oxygen Delivery

The rate of oxygen transport in arterial blood is called the *oxygen delivery* (DO_2), and is the product of the cardiac output and the oxygen concentration in arterial blood (CaO_2).

$$DO_2 = CO \times CaO_2 \tag{8.10}$$

The O_2 concentration in arterial blood (CaO_2) is a function of the hemoglobin concentration (Hb), the O_2 carrying capacity of hemoglobin (1.34 mL per gram), and the arterial oxyhemoglobin saturation (SaO_2): i.e., $CaO_2 = 1.34 \times Hb \times SaO_2$. Therefore, the DO_2 equation can be rewritten as:

$$DO_2 = CO \times (1.34 \times Hb \times SaO_2) \tag{8.11}$$

The size-adjusted DO_2 is calculated using the cardiac index instead of cardiac output, and it is expressed as mL/min/m^2. The normal range is shown in Table 8.1

Oxygen Uptake

Oxygen uptake (VO_2), also called *oxygen consumption*, is the rate at which oxygen is taken up from the systemic capillaries into the tissues. The VO_2 is calculated as the product of the cardiac

output (CO) and the difference in O_2 concentration between arterial and venous blood ($CaO_2 - CvO_2$). The venous blood in this instance is "mixed" venous blood in the pulmonary artery.

$$VO_2 = CO \times (CaO_2 - CvO_2) \tag{8.12}$$

If the CaO_2 and CvO_2 are each broken down into their component parts, the VO_2 equation can be rewritten as:

$$VO_2 = CO \times 1.34 \times Hb \times (SaO_2 - SvO_2) \tag{8.13}$$

SaO_2 and SvO_2 are the oxyhemoglobin saturations in arterial and mixed venous blood, respectively. The SaO_2 is continuously monitored with pulse oximetry, and the SvO_2 can also be continuously monitored with specialized PA catheters (mentioned earlier). The SvO_2 can also be measured in a blood sample drawn through the distal port of the PA catheter.

The size-adjusted VO_2 is calculated using the cardiac index instead of the cardiac output, and it is expressed as mL/min/m^2. The normal range is shown in Table 8.1. Note that the VO_2 is much lower than the DO_2 (see next).

Oxygen Extraction Ratio

The oxygen extraction ratio (O_2 ER) is the ratio of O_2 uptake to O_2 delivery:

$$O_2 \text{ ER} = VO_2/DO_2 \tag{8.14}$$

The normal range for the O_2 ER is 0.2 to 0.3, which means that O_2 uptake into tissues represents only 20% to 30% of the O_2 delivered to the systemic microcirculation. Oxygen extraction can increase to 0.50 or even higher to compensate for decreases in O_2 delivery. (See Chapter 9 for a more detailed explanation of this topic.)

Applications

The following are some examples of clinical situations where the information generated by PA catheters can be useful:

. The management of acute, decompensated heart failure, especially when complicated by labile blood pressures or worsening renal function.

. Perioperative management of patients undergoing cardiac surgery.

. The management of circulatory shock (24), especially cardiogenic shock, where use of the PA catheter has had some success in improving outcomes (25).

. Identifying responsiveness to volume infusion (6).

. Determining the need for, and response to, erythrocyte transfusions (see Chapter 12). Ditto for oxygen therapy (see Chapter 25).

. Identifying occult cases of weaning-induced cardiac dysfunction (26) in patients who have difficulty weaning from mechanical ventilation.

The measurements generated by PA catheters will appear in many chapters in this book, including Chapter 9 (Systemic Oxygenation), Chapter 11 (Fluid Management), Chapter 12 (Anemia and Red Blood Cell Transfusions), Chapters 14–17 (Shock Syndromes), Chapter 18 (Acute Heart Failure), Chapter 25 (Oxygen Inhalation), Chapter 26 (Noninvasive Ventilation), and Chapter 30 (Discontinuing Mechanical Ventilation).

A FINAL WORD

An Undeserved Reputation

Despite the wealth of physiologically relevant information it provides, the PA catheter has been vilified and almost abandoned because clinical studies have shown no survival benefit associated with use of the catheter (3). The following are some points in support of the PA catheter.

. First and foremost, *the PA catheter is a monitoring device, not a therapy*, and clinical outcomes (e.g., mortality rate) should be used to evaluate therapies, not measurements.

. Surveys indicate that *physicians often don't understand the measurements provided by PA catheters* (27,28), and any tool can be ineffective in the wrong hands.

. Finally, the incessant use of mortality rates to evaluate critical care interventions is problematic because *the presumption that every intervention has to save lives to be of value is not valid*. Interventions have more specific and immediate goals other than life or death (e.g., the goal of a vasopressor drug infusion is to increase the blood pressure). In the case of a monitoring device, the goal is to provide useful information, and the PA catheter achieves this goal with distinction.

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Chapter 9

Systemic Oxygenation

If one were to name the universal factor in all death…
it would certainly be loss of oxygen.

Sherwin Nuland, MD (*a*)

The management of critically ill patients is dominated by interventions that promote tissue oxygenation, yet it is not possible to monitor tissue O_2 levels in a clinical setting. Instead, tissue oxygenation is evaluated indirectly using global measures of systemic oxygen transport (i.e., O_2 delivery and O_2 uptake) along with a presumed marker of inadequate tissue oxygenation (i.e., the plasma lactate level). This chapter describes these measures, and how they are used (and misused). The information in this chapter is part of the core knowledge base in critical care; i.e., the knowledge that distinguishes ICU-level care from patient care on a general medical or surgical service.

OXYGEN IN BLOOD

The relevant measures of oxygen (O_2) in blood include the partial pressure of O_2 (PO_2), the O_2 saturation of hemoglobin (SO_2), the concentrations of hemoglobin-bound O_2 and dissolved O_2, and the total O_2 concentration (also called the O_2 content). The reference values for these measures in arterial and venous blood are shown in Table 9.1.

TABLE 9.1 Normal Measures of Oxygen in Arterial and Venous Blood

Measure	Arterial Blood	Venous Blood
Partial Pressure of O_2	90 mm Hg	40 mm Hg
O_2 Saturation of Hb	98%	73%
Hb-bound O_2	19.7 mL/dL	14.7 mL/dL
Dissolved O_2	0.27 mL/dL	0.1 mL/dL

Total O_2 Content[1]	20 mL/dL	15 mL/dL
Blood Volume[2]	1.25 L	3.75 L
Total Volume of O_2	250 mL	555 mL

Values shown are for a body temperature of 37 °C and a hemoglobin concentration of 15 g/dL.

[1]Numbers rounded to nearest whole number.

[2]Volume estimates based on a total blood volume of 5 Liters, with 25% of the volume in arteries and 75% in veins.

Oxyhemoglobin Dissociation Curve

The oxygenation of the hemoglobin pool is expressed as the *oxygen saturation of hemoglobin* (SO_2), and is the fraction of the hemoglobin pool that is fully saturated with oxygen. The SO_2 is measured (by oximetry) as the ratio of oxygenated hemoglobin to total hemoglobin. (See Chapter 7 for a description of oximetry.) The principal determinants of SO_2 are the PO_2 in blood, and the affinity of hemoglobin for binding O_2. These relationships are described by the oxyhemoglobin dissociation curve, which is shown in Figure 9.1. The "S" shape of the curve offers two advantages. First, the arterial PO_2 (PaO_2) is normally on the upper, flat part of the curve, which means that a large drop in PaO_2 (down to 60 mm Hg) results in only minor changes in the oxygenation of hemoglobin (the SO_2). Secondly, the venous PO_2 (which is ≈40 mm Hg) is on the steep portion of the curve, which facilitates O_2 uptake in the pulmonary capillaries.

SHIFTS IN THE CURVE: A number of conditions can alter the affinity of hemoglobin for O_2 and thereby shift the position of the oxyhemoglobin dissociation curve. These conditions are listed in Figure 9.1. A shift of the curve to the right facilitates O_2 release in tissues, while a shift to the left impedes O_2 release. The position of the curve is indicated by the P50, which is the PO_2 that corresponds to an SO_2 of 50%. The P50 is normally about 27 mm Hg (1), and will increase when the curve shifts to the right, and decrease when the curve shifts to the left. For example, a decrease in the P50 to 15 mm Hg (indicating a leftward shift of the curve) has been reported in blood that is stored in acid-citrate-dextrose (ACD) preservative for 3 weeks, and is attributed to depletion of 2,3 diphosphoglycerate (2,3-DPG) in the red blood cells (2).

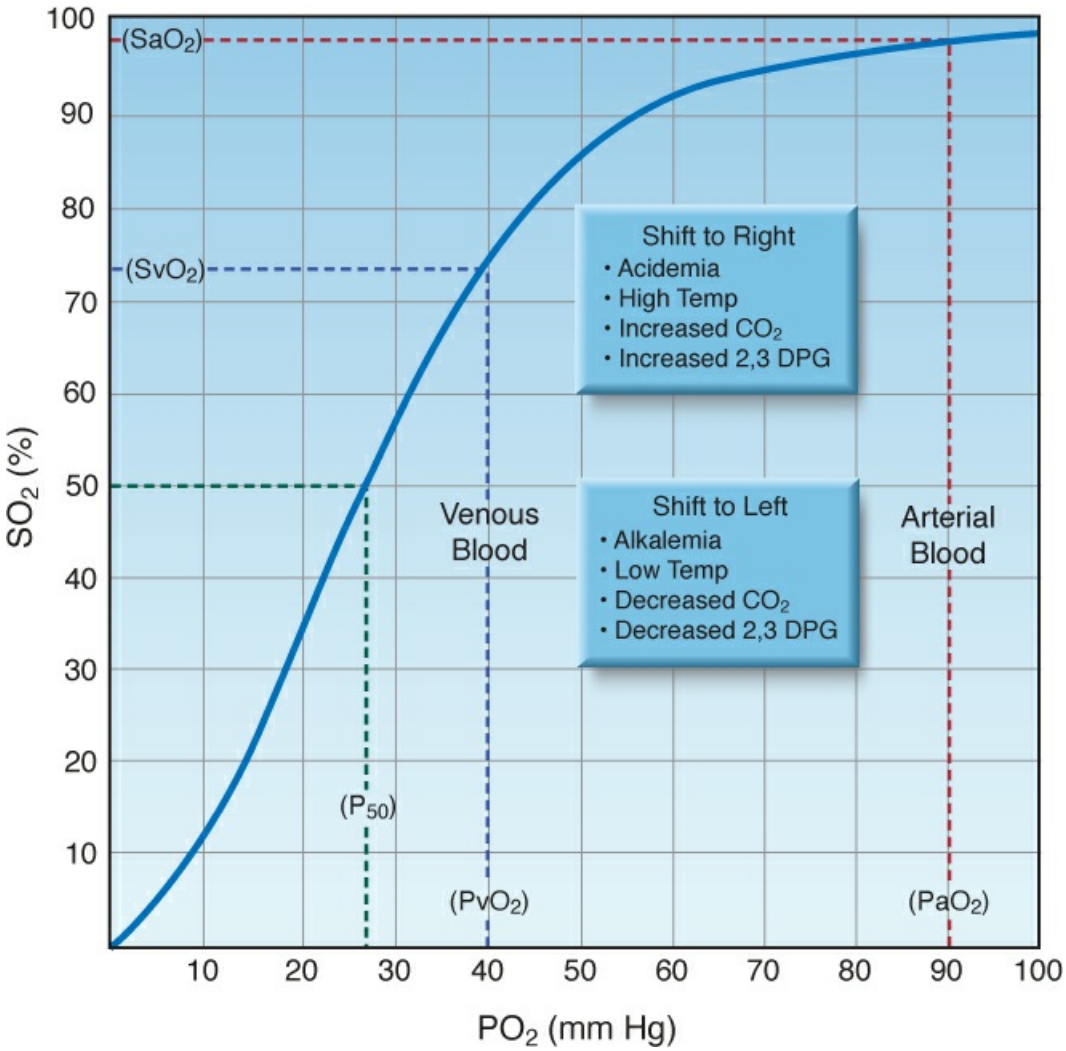

FIGURE 9.1 Oxyhemoglobin dissociation curve showing the normal relationship between the PO_2 in blood and the O_2 saturation of hemoglobin (SO_2). The P_{50} is the PO_2 that corresponds to an SO_2 of 50%. Abbreviations: PaO_2 = arterial PO_2, PvO_2 = venous PO_2, SaO_2 = arterial SO_2, SvO_2 = venous SO_2.

Shifts in the oxyhemoglobin dissociation curve have opposing effects in the pulmonary and systemic capillaries; i.e., a shift to the left impedes O_2 release systemically but facilitates O_2 uptake in the lungs. Therefore, the significance of these shifts for overall O_2 exchange is unclear.

Oxygen Content of Blood

The concentration (content) of O_2 in blood is the summed contribution of the O_2 that is bound to hemoglobin and the O_2 that is dissolved in plasma.

Hemoglobin-Bound Oxygen

The concentration of hemoglobin-bound O_2 (HbO_2) is determined by the concentration of hemoglobin [Hb] (usually expressed as grams per deciliter (100 mL), the O_2 binding capacity of hemoglobin (which is 1.34 mL O_2 per gram Hb), and the O_2 saturation of hemoglobin (SO_2).

This relationship is expressed as follows (3):

$$HbO_2 = 1.34 \times [Hb] \times SO_2 \text{ (mL/dL)} \quad (9.1)$$

(The SO_2 in this equation is expressed as a decimal rather than percentage: e.g., 0.75 instead of 75%.)

Dissolved Oxygen

Plasma is about 93% water, and oxygen does not readily dissolve in water (which is why hemoglobin is needed as an O_2 carrier). The solubility of O_2 in plasma is temperature-dependent, and varies inversely with a change in body temperature. At a normal body temperature (37 °C), each increment in PO_2 of 1 mm Hg will increase the concentration of dissolved O_2 in plasma by 0.03 mL/L (4). This is expressed as a *solubility coefficient* of 0.03 mL/L/mm Hg (or 0.003 mL/dL/mm Hg) The concentration of dissolved O_2 in plasma at 37 °C is then determined as follows:

$$\text{Dissolved } O_2 = 0.003 \times PO_2 \text{ (mL/dL)} \quad (9.2)$$

This equation emphasizes the limited volume of dissolved O_2 in the physiological PO_2 range (see next).

Arterial O_2 Content

The O_2 content in arterial blood (CaO_2) is determined by combining Equations 9.1 and 9.2 and inserting the SO_2 and PO_2 of arterial blood (SaO_2 and PaO_2): i.e.,

$$CaO_2 = (1.34 \times [Hb] \times SaO_2) + (0.003 \times PaO_2) \text{ (mL/dL)} \quad (9.3)$$

Using normal values for {Hb] (15 g/dL), SaO_2 (0.98), and PaO_2 (90 mm Hg) yields the following:

$$CaO_2 = (19.7) + (0.27) \quad (9.4)$$

Thus, the normal arterial O_2 content is about 20 mL/dL (or 200 mL/L), and *only 1.5% represents dissolved oxygen*.

Anemia vs. Hypoxemia

The relative impact of anemia and hypoxemia on the arterial O_2 content (CaO_2) is shown in Figure 9.2. Note that a 50% reduction in [Hb] (from 15 to 7.5 g/dL) results in an equivalent 50% reduction in CaO_2 (from 20 to 10 mL/dL), while a 50% reduction in the PaO_2 (from 90 to 45 mm Hg, corresponding to a decrease in SaO_2 from 98% to 78%) results in only a 20% decrease in CaO_2 (from 20 to 16 mL/dL). This demonstrates that *anemia has a much greater influence on arterial oxygenation than hypoxemia*.

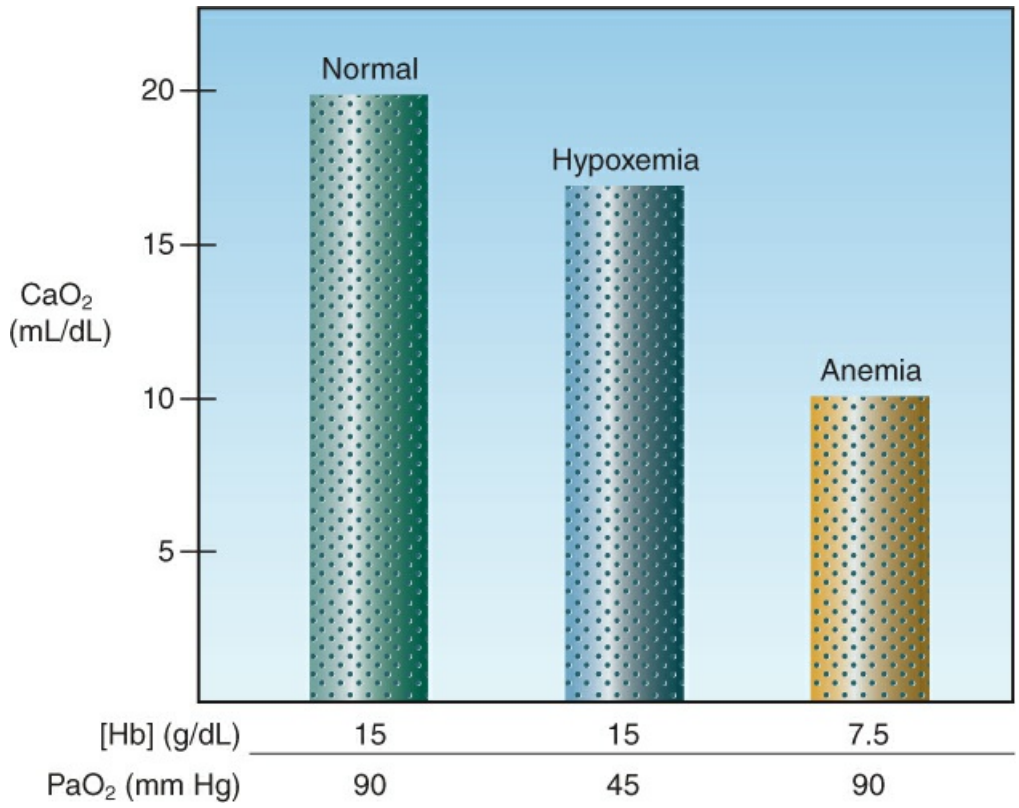

FIGURE 9.2 The influence of proportional degrees of anemia and hypoxemia on the oxygen content in arterial blood (CaO_2).

Venous O_2 Content

The venous O_2 content (CvO_2) represents the O_2 content in "mixed" venous blood (from the right heart or pulmonary artery). The equation describing CvO_2 is similar in format to Equation 9.3, but the SO_2 and PO_2 are for mixed venous blood (SvO_2 and PvO_2).

$$CvO_2 = (1.34 \times [Hb] \times SvO_2) + (0.003 \times PvO_2) \quad (9.5)$$

As shown in Table 9.1, the normal mixed venous O_2 content is about 15 mL/dL, and less than 1% (0.1 mL/dL) represents dissolved O_2. Note also that the difference between the arterial and venous O_2 content ($CaO_2 - CvO_2$) is 5 mL/dL, or 50 mL/L, which means that 50 mL of O_2 is extracted from each liter of blood flowing through the capillaries. At a normal cardiac output of 5 L/min, the O_2 extracted from capillary blood would be $5 \times 50 = 250$ mL/min, which is the normal O_2 consumption in an adult at rest. This demonstrates how *the oxygenation of blood can provide information about the oxygen utilization in tissues.*

Simplified O_2 Content Equation

The dissolved O_2 is such a small fraction of the total O_2 content that it is usually eliminated from the equation describing O_2 content, as shown below.

$$O_2 \text{ Content} = 1.34 \times [Hb] \times SO_2 \quad (9.6)$$

Volume Distribution of O_2 in Blood

Although the O_2 content in arterial blood exceeds that in venous blood, the volume of O_2 (i.e., the product of the O_2 content and blood volume), in arterial blood is far lower than in venous blood. This is shown in Table 9.1, where the volume of O_2 in arterial blood (250 mL) is less than half the volume in venous blood (555 mL). This is a reflection of the uneven distribution of blood volume in arteries and veins: i.e., the arteries contain only 25% of the total blood volume, while the remaining 75% is in the venous circulation. Thus, of the total volume of O_2 in the blood (250 + 555 = 805 mL), about 70% (555/805) is not available for aerobic metabolism because it is in the venous circulation.

OXYGEN TRANSPORT

The transport of O_2 from the lungs to metabolizing tissues is described by three parameters: the rate of O_2 delivery in arterial blood (O_2 delivery), the rate of O_2 uptake from the systemic microcirculation (O_2 uptake), and the fractional extraction of O_2 from capillary blood (O_2 extraction ratio). The reference ranges for these measures are listed in Table 9.2, including both absolute and size-adjusted ranges. The preferred measure of body size for hemodynamic parameters is the body surface area (BSA) in square meters (m^2). (See Equation 8.3 for the calculation of BSA.) An average-sized adult has a BSA of about 1.7 m^2.

TABLE 9.2 Normal Ranges for Oxygen Transport Parameters

Parameter	Absolute Range	Size-Adjusted Range†
Cardiac Output	5–6 L/min	2.4–4.0 L/min/m^2
O_2 Delivery	900–1,100 mL/min	520–600 mL/min/m^2
O_2 Uptake	200–270 mL/min	110–160 mL/min/m^2
O_2 Extraction Ratio	0.2–0.3	

†Size-adjusted values are the absolute values divided by the patient's body surface area in square meters (m^2).

Oxygen Delivery (DO_2)

The rate of O_2 delivery in arterial blood (DO_2) is the product of the cardiac output (CO) and the O_2 content of arterial blood (CaO_2) (5); i.e.,

$$DO_2 = CO \times CaO_2 \times 10 \text{ (mL/min)} \quad (9.7)$$

(The multiplier of 10 is used to convert the CaO_2 from mL/dL to mL/L.) If the CaO_2 is broken down into its components (1.34 × [Hb] × SaO_2), Equation 9.7 can be rewritten as:

$$DO_2 = CO \times (1.34 \times [Hb] \times SaO_2) \times 10 \quad (9.8)$$

Three measurements are needed to calculate the DO_2: cardiac output, hemoglobin concentration, and arterial O_2 saturation. If the DO_2 is expressed in relation to body size (BSA), the "cardiac index" (CI = CO/BSA) is used instead of the cardiac output. The DO_2 in healthy adults at rest is 900–1,100 mL/min, or 500–600 mL/min/m^2 when ad-justed for body size.

Oxygen Uptake

The rate of O_2 transport from the systemic capillaries into the tissues is called the *oxygen uptake* (VO_2). Since oxygen is not stored in tissues, the VO_2 is also a measure of the *oxygen consumption* in systemic tissues. The VO_2 can be calculated as the product of the cardiac output (CO) and the difference between arterial and venous O_2 content ($CaO_2 - CvO_2$).

$$VO_2 = CO \times (CaO_2 - CvO_2) \times 10 \text{ (mL/min)} \quad (9.9)$$

(The multiplier of 10 is included for the same reason as explained for the DO_2.) This equation is a modified version of the Fick equation for cardiac output (i.e., $CO = VO_2 / CaO_2 - CvO_2$), and has been called the *reverse Fick method* (6). The CaO_2 and CvO_2 in Equation 9.9 share a common term (1.34 × [Hb]), so the equation can be restated as:

$$VO_2 = CO \times 1.34 \times [Hb] \times (SaO_2 - SvO_2) \times 10 \quad (9.10)$$

Thus, four measurements are required to calculate the VO_2: the same 3 measurements used to calculate the DO_2, plus the O_2 saturation in "mixed" venous blood in the pulmonary arteries (SvO_2), which requires a pulmonary artery catheter. When the VO_2 is expressed in relation to body size (BSA), the "cardiac index" (CI = CO/BSA) is used instead of the cardiac output. The VO_2 in healthy adults at rest is 200–300 mL/min, or 110–160 mL/min/m^2.

Variability

Each of the 4 measurements used to derive the VO_2 has an inherent variability, and these are shown in Table 9.3 (6–8). The variability of the calculated VO_2 is ±18%, which is the summed variability of the individual components. Therefore, *the VO_2 that is calculated from the modified Fick equation must change by at least 18% for the change to be considered significant.*

Calculated vs. Measured VO_2

The calculated VO_2 is not the whole-body VO_2 because it does not include the VO_2 of the lungs. Normally, the VO_2 of the lungs accounts for less than 5% of the whole-body VO_2 (9), but it can make up 20% of the whole body VO_2 when there is inflammation in the lungs (10).

MEASURED VO_2: The measurement of the whole body VO_2 involves simultaneous measurements of the O_2 concentration in inhaled and exhaled gas. This requires an instrument that is equipped with an oxygen analyzer, such as the "metabolic carts" used for indirect calorimetry (see Chapter

48). The O_2 analyzer is connected to the proximal airway (usually in intubated patients) to record the fractional concentration of O_2 in inhaled and exhaled gas (F_IO_2 and F_EO_2). The instrument also records the minute ventilation (V_E), and the VO_2 is derived as follows:

$$VO_2 = VE \times (F_IO_2 - F_EO_2) \quad (9.11)$$

The measured VO_2 has a reported variability of ±5% (6,8), which is much less than the variability of the calculated VO_2 (±18%). The major drawback of the VO_2 measurement is the need for specialized equipment and trained personnel, which limits availability.

TABLE 9.3 Variability of Measurements Used to Calculate the Oxygen Consumption

Measurement	Variability
Thermodilution Cardiac Output	± 10%
Hemoglobin Concentration	± 2%
O_2 Saturation of Hemoglobin	± 2%
O_2 Content of Blood	± 4%
CaO_2–CvO_2	± 8%
Calculated VO_2	± 18%
Measured VO_2	± 5%

From References 6–8.

Oxygen Extraction Ratio

The fractional uptake of O_2 into tissues is expressed as the *oxygen extraction ratio* (O_2ER), which is the ratio of O_2 uptake (VO_2) to O_2 delivery (DO_2).

$$O_2ER = VO_2 / DO_2 \quad (9.12)$$

This ratio can be multiplied by 100 and expressed as a percentage. The VO_2 and DO_2 share common terms (Q × 1.34 x [Hb] x 10), which allows Equation 9.12 to be restated as follows:

$$O_2ER = (SaO_2 - SvO_2) / SaO_2 \quad (9.13)$$

If the SaO_2 is close to 100% (close to 1.0), the denominator in Equation 9.13 can be eliminated; i.e.,

$$O_2ER = (SaO_2 - SvO_2) \quad (9.14)$$

or the equation can be futher simplified to include only a single variable:

$$O_2ER = 1 - SvO_2 \quad (9.15)$$

The VO_2 is normally about 25% of the DO_2, so the normal O_2ER is 0.25 (range = 0.2–0.3), as shown in Table 9.2. Thus, *only 25% of the O_2 delivered to the capillaries is taken up into the tissues* when conditions are normal. This changes when O_2 delivery is reduced, as described next.

OXYGEN EXTRACTION

The oxygen transport system operates to maintain a constant VO_2 in the face of decreases in O_2 delivery (DO_2), and this is accomplished by compensatory increases in the O_2 extraction ratio (O_2ER) (11). This is explained by rearranging the terms in Equation 9.12 so that VO_2 is the derived variable:

$$VO_2 = DO_2 \times O_2ER \tag{9.16}$$

This equation predicts that the VO_2 will remain constant when DO_2 is decreased if there is an proportional increase in O_2 extraction. However, if the increase in O_2 extraction cannot fully compensate for a decrease in DO_2, then the VO_2 will begin to decrease, and this marks the onset of oxygen-limited (anaerobic) metabolism.

The relationships in Equation 9.16 are illustrated in Figure 9.3. The graph shows the effects of a progressive decrease in DO_2 on the VO_2, and the boxes show the O_2 extraction at relevant points on the curve. In this case, O_2 extraction is represented by the (SaO_2–SvO_2) difference, which is allowed because the SaO_2 is typically maintained at >90% (i.e., close to 1.0). This creates the following relationships:

$$VO_2 = DO_2 \times (SaO_2 - SvO_2) \tag{9.17}$$

The graph indicates that, as DO_2 decreases below normal (moving to the left along the curve), the VO_2 initially remains unchanged, indicating that there is a compensatory increase in (SaO_2–SvO_2). However, a point is eventually reached where the VO_2 begins to decrease, and at this point, the (SaO_2–SvO_2) difference has increased from 25% to 50%. Beyond this point, the VO_2 decreases in response to a decrease in DO_2, indicating that O_2 extraction is no longer able to fully compensate for the declining DO_2. The point where the VO_2 becomes “delivery-dependent” is the threshold for O_2-limited metabolism (12).

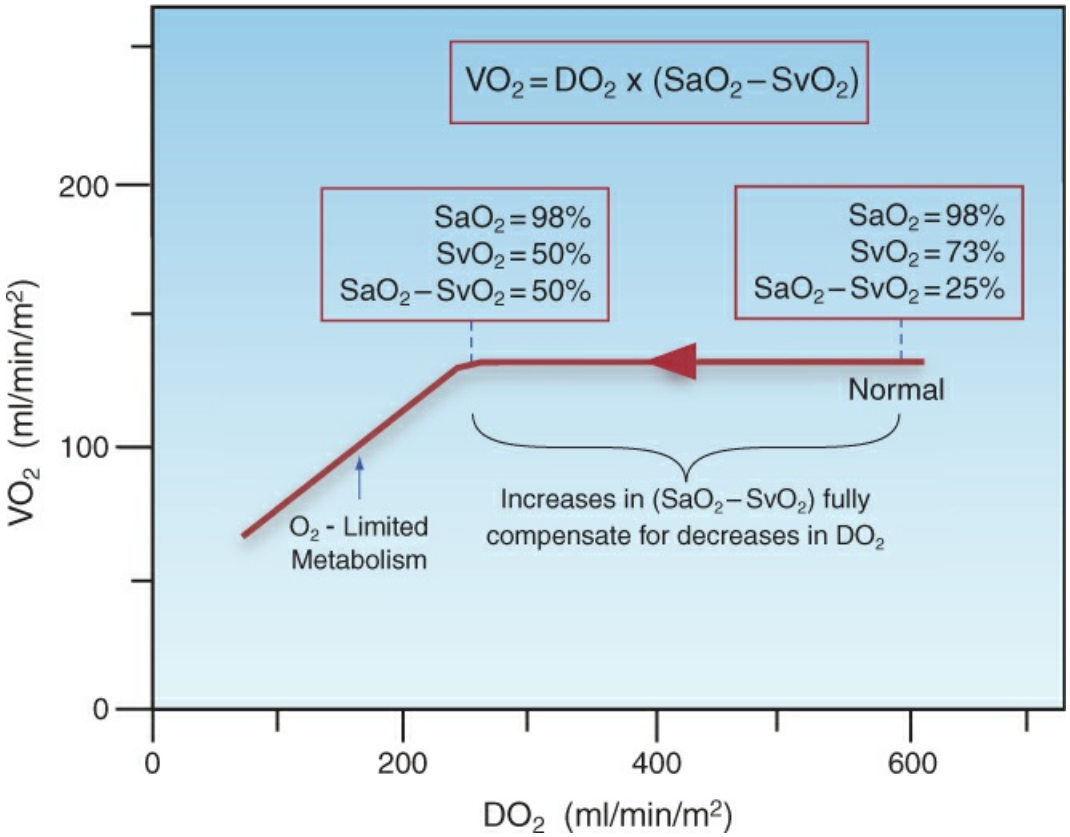

FIGURE 9.3 Graph showing the relationship between O_2 delivery (DO_2) and O_2 uptake (VO_2). The O_2 extraction ratio (O_2ER) is represented by (SaO_2 – SvO_2) difference. See text for explanation).

The relationships in Figure 9.3 indicate that the (SaO_2–SvO_2) difference can be used to assess the balance between O_2 delivery and O_2 consumption, and more importantly, to identify when tissue oxygenation is threatened or impaired.

The (SaO_2 – SvO_2) Difference

As shown in Equation 9.14, the (SaO_2–SvO_2) difference can be used as a measure of O_2 extraction as long as the SaO_2 exceeds 90%. The following are some guidelines for the interpretation of the (SaO_2–SvO_2) difference, which are summarized in Table 9.4. (*Note:* O_2 extraction is influenced by the metabolic rate, and the following guidelines are valid only if the metabolic rate is normal.)

. The normal (SaO_2– SvO_2) is 20–30%.

. An increase in (SaO_2– SvO_2) above 30% indicates a decrease in O_2 delivery (from hypoxemia, anemia, or decreased cardiac output).

. An increase in (SaO_2– SvO_2) to ≥50% indicates that tissue oxygenation is threatened or impaired. This has been validated in animal studies (13).

. A decrease in (SaO_2– SvO_2) to <20% indicates a defect in O_2 utilization in tissues, which is

usually the result of sepsis. This condition has also been called “peripheral shunting”, since it mimics the changes produced by peripheral arteriovenous shunts.

The SaO_2 is monitored continuously with pulse oximetry (which is mandatory in ICU patients), and the SvO_2 is measured in “mixed venous” blood in the pulmonary arteries, which requires a pulmonary artery (PA) catheter. The SvO_2 can be monitored continuously with specialized PA catheters capable of venous oximetry (e.g., Triox™-PAC, ICU Medical, San Clemente, CA). The technique of venous oximetry is described in Chapter 7, and illustrated in Figure 7.5.

Venous O_2 Saturation (SvO_2)

When the SaO_2 approaches 100%, the SvO_2 can be used alone to evaluate O_2 extraction, as described in Equation 9.15. This equation demonstrates that the SvO_2 varies inversely with changes in O_2 extraction: e.g., an increase in O_2 extraction will result in a decrease in SvO_2. The following are some guidelines for interpreting the SvO_2, which are summarized in Table 9.4.

. The normal range for SvO_2 in pulmonary artery blood is 65–75% (14).

. The SvO_2 varies spontaneously by an average of 5% (15), so a change in SvO_2 should exceed 5% to be considered significant.

. A decrease in SvO_2 to <65% indicates a decrease in O_2 delivery (from hypoxemia, anemia, or decreased cardiac output).

. A decrease in SvO_2 to ≤50% indicates that tissue oxygenation is threatened or impaired (16).

. An SvO_2 that is 80% or higher is a sign of impaired O_2 utilization in metabolizing tissues, and is usually the result of sepsis.

TABLE 9.4 Surrogate Measures of O_2 Extraction

Measure	Normal Range	Tissue O_2 Threatened	Defect in O_2 Utilization
$SaO_2 - SvO_2$	20-30%	≥50%	<20%
SvO_2	65-75%	≤50%	>80%

Central Venous O_2 Saturation ($ScvO_2$)

The decline in popularity of pulmonary artery catheters has shifted attention to the O_2 saturation in the superior vena cava; i.e., the “central venous O_2 saturation” ($ScvO_2$). The relevant information about $ScvO_2$ is summarized in the following statements.

. The $ScvO_2$ is lower than the SvO_2 in healthy subjects. However, it is higher than the SvO_2 (by an average of 7%) in critically ill patients (14,17), and this difference can be as high as 18% in patients with circulatory shock (17,18). The $ScvO_2$ is heavily influenced by the cerebral

venous O_2 saturation, and the elevated $ScvO_2$ in circulatory shock is attributed to peripheral vasoconstriction with relative preservation of cerebral blood flow.

. Despite the discrepancy between $ScvO_2$ and SvO_2, changes in $ScvO_2$ generally mirror those in the SvO_2 (17), and *trends in the $ScvO_2$ are considered more reliable than individual measurements* (19). The definition of a significant change in $ScvO_2$ is the same as that mentioned for the SVO_2 (i.e., Δ >5%).

. The normal range of $ScvO_2$ is not well defined, but an $ScvO_2$ of 70% is one of the recommended goals of hemodynamic management in circulatory shock (20).

The $ScvO_2$ can be monitored with central venous catheters or peripherally-inserted central catheters (PICCs); both catheters are available as oximetry catheters (e.g., Triox™-CVC and Triox™-PICC, ICU Medical, San Clemente, CA) that provide continuous $ScvO_2$ monitoring.

Tissue O_2 Saturation (StO_2)

The technique of *near-infrared spectroscopy* (NIRS) is a form of oximetry that uses an optical probe on the skin to measure the O_2 saturation of hemoglobin in the microcirculation of the underlying tissue. This measurement is known as the *tissue O_2 saturation* (StO_2), which is a misleading term because the measured variable is mostly in blood. Since most of the blood in the microcirculation is in the venules, the StO_2 is primarily a reflection of venous O_2 saturation (SvO_2 or $ScvO_2$) (21). (The StO_2 in muscle can also be influenced by the O_2 saturation of myoglobin) (22).

In adults, NIRS has been used to monitor the StO_2 in the cerebral cortex (23) and in skeletal muscle (24). In patients with circulatory shock, there is a close correlation between changes in skeletal muscle StO_2 and changes in systemic O_2 delivery (DO_2), suggesting that StO_2 monitoring could serve as a noninvasive means of tracking changes in O_2 delivery (24).

One of the major limitations of the StO_2 measurement is the inability to define normal and abnormal levels, since there is a marked variability in the StO_2 in healthy subjects, and in patients with circulatory shock (25). This could be a reflection of the methodology, because photons scatter in tissues (i.e., they do not follow a straight path from light source back to the photodetector), and the degree of scatter can vary greatly in individual subjects and in different pathological states.

LACTATE

An increase in the plasma lactate concentration (>2 mmol/L) is considered the most reliable marker of inadequate tissue oxygenation, and it is a stated requirement for the diagnosis of circulatory shock (26). However, the traditional concepts about lactate are changing, as explained in this section.

Lactate and Survival

Clinical studies have consistently shown that the mortality rate in critically ill patients is directly

related to the initial plasma lactate level, and to the time required for the lactate level to return to normal after treatment is initiated. This is demonstrated in Figure 9.4. The graph on the left shows the relationship between the initial lactate level and in-hospital mortality (27), and the graph on the right shows the relationship between mortality and the time required to normalize the plasma lactate (called "lactate clearance") (28).

The relationship between plasma lactate levels and survival highlights the importance of monitoring plasma lactate in critically ill patients. However, this relationship is *not* evidence that lactate is a marker of inadequate tissue oxygenation, as explained next.

Circular Reasoning

The relationship between plasma lactate levels and survival is considered evidence that lactate is a marker of inadequate tissue oxygenation because of the popular notion that oxygen deprivation is the universal source of cell death in critically ill patients. However, this notion is largely *based* on the relationship between plasma lactate levels and survival.

Contrary Evidence

Because of the difficulties in recording the PO_2 in cells (and especially in mitochondria), there is no evidence that cell death in critically ill patients is the result of O_2 deprivation. However, there is evidence to the contrary: i.e., in animal studies using a positron-emitting marker of cell hypoxia (18F-fluoromisonidazole), there was no evidence of cell hypoxia in any of the major organs in septic shock (29), and human studies using PO_2 recordings from skeletal muscle have reported that *tissue PO_2 levels are actually increased in patients with septic shock* (30,31).

Considering that the intracellular PO_2 in skeletal muscle averages 5 mm Hg, and can be <1 mm Hg (32), while the recorded PO_2 in cardiac myocytes is 0.2–2.4 mm Hg (33), it seems that cells normally operate at very low PO_2 levels, which is contrary to the idea that cell death is the result of low PO_2 levels. In fact, an oxygen-poor environment in cells is advantageous because it limits the risk of oxidative cell injury.

The observations just presented suggest that cellular O_2 deprivation may not be the universal culprit in cell death (and organ failure) in critically ill patients, and this implies that aerobic lactate production may be much more common than suspected (see next).

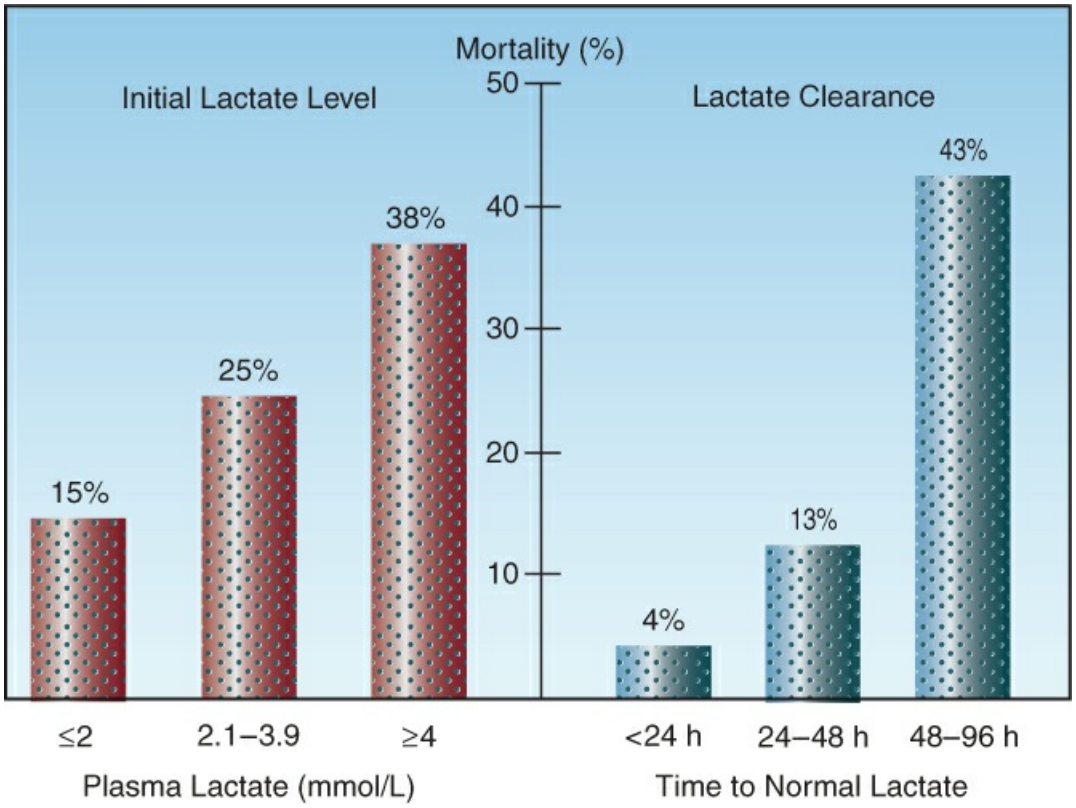

FIGURE 9.4 Graphs showing the relationship between plasma lactate levels and in-hospital mortality in critically ill patients. The graph on the left shows the relationship between the initial lactate level and mortality (27), and the graph on the right shows the relationship between the mortality rate and the time for increased lactate levels to normalize (lactate clearance) (28).

Aerobic Lactate Production

The role of aerobic lactate production is explained using the pathways of glucose metabolism in Figure 9.5. There are two general pathways for glucose metabolism: one is located in the cytoplasm, and is known as *glycolysis*, and the other is located in mitochondria, and is involved in *oxidative phosphorylation* (i.e., the production of ATP). The glycolytic pathway operates in the presence or absence of oxygen, while the mitochondrial pathway proceeds only in the presence of oxygen. The traditional teaching is that glycolysis reaches a pivotal point with the formation of pyruvate: when O_2 is available, pyruvate moves into mitochondria via the enzyme pyruvate dehydrogenase, and when O_2 is not available, pyruvate is reduced to lactate using the enzyme lactate dehydrogenase (LDH).

According to the scheme just presented, pyruvate is the end-point of aerobic glycolysis, and lactate is the end-point of anaerobic glycolysis. However this is not the case, because lactate is produced under aerobic conditions: i.e., the daily production of lactate averages about 20 mmol/kg body weight (34). In fact, the reaction that converts pyruvate to lactate has an equilibrium constant that strongly favors lactate formation. The aerobic production of lactate is enhanced in several clinical conditions, including those listed in Table 9.5. Many of the conditions in this table are likely to be encountered in critically ill patients, including those described next.

TABLE 9.5 Sources of Aerobic Hyperlactatemia	
Conditions	**Drugs and Toxins**
Asthma (severe)	β Agonists
Ketoacidosis	Catecholamines
Liver Dysfunction	Cyanide
Seizures	Metformin
Sepsis	Propofol
Stress	Propylene Glycol
Thiamine Deficiency	Salicylates
Tumors	Toxic Alcohols

Sepsis

Hyperlactatemia is considered a universal consequence of sepsis and septic shock (26, 35), and two sources of this phenomenon have been identified. The principal source is inhibition of the pyruvate dehydrogenase (PDH) enzyme that allows pyruvate to enter mitochondria and fuel oxidative phosphorylation (see Figure 9.5) (36). The culprits in this inhibition are bacterial products (e.g., endotoxin) and proinflammatory cytokines (37,38). The result is enhanced lactate production that is not the result of cellular hypoxia. Sepsis-induced inhibition of the PDH enzyme would explain why the cell injury in sepsis is attributed to a defect in O_2 utilization in mitochondria (38). Sepsis is also associated with a catecholamine-driven increase in the rate of glycolysis (39), and this (especially when combined with inhibition of the PDH enzyme) is the second source of aerobic lactate production in sepsis.

As just described, there is considerable evidence that the hyperlactatemia in sepsis is the result of aerobic (not anaerobic) lactate production. Considering that sepsis is the leading cause of in-hospital deaths in the United States (40), it is reasonable to conclude that aerobic hyperlactatemia is much more common than suspected in critically ill patients.

Physiological Stress

Stressful conditions are associated with an increase in glucose uptake into cells, which is attributed to the accumulation of a glucose transporter protein at the cell surface (41). This effect, combined with the stimulatory effect of catecholamines mentioned previously (39), results in a considerable (40–50%) increase in the rate of aerobic glycolysis, and a subsequent increase in aerobic lactate production (29).

Thiamine Deficiency

The PDH enzyme that draws pyruvate into the mitochondrion (and thereby fuels oxidative phosphorylation) requires thiamine pyrophosphate (TPP) as a cofactor (see Figure 9.5), and deficiency of this cofactor will divert pyruvate to the production of lactate and enhance aerobic lactate production. This is the mechanism for the hyperlactatemia in thiamine deficiency (42), which is considered a common and often unrecognized condition in critically ill patients (43).

(See Chapter 48 for more on thiamine deficiency.)

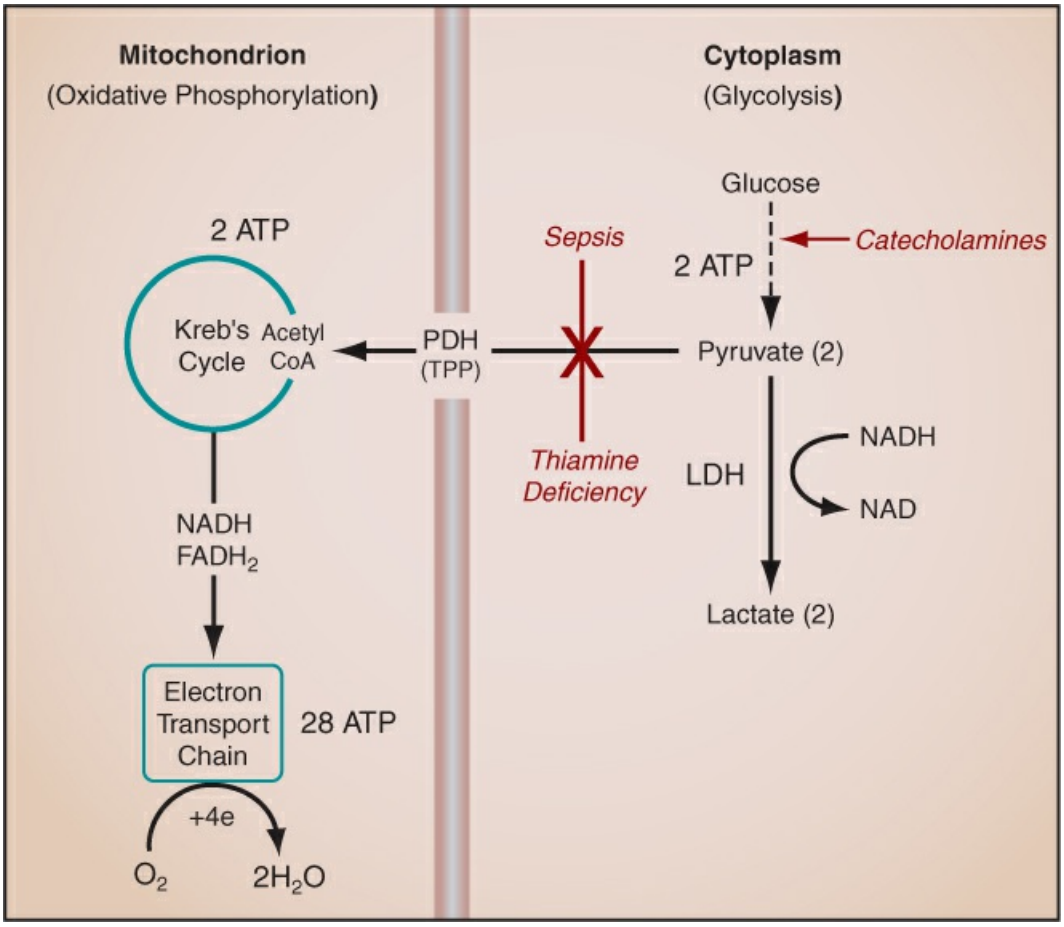

FIGURE 9.5 The pathways of glucose metabolism. ATP = adenosine triphosphate, PDH = pyruvate dehydrogenase, TPP = thiamine pyrophosphate, LDH = lactate dehydrogenase, NAD and NADH = nicotinamide adenine dinucleotide (oxidized and reduced), $FADH_2$ = flavin adenine dinucleotide (reduced). See text for further explanation.

Conclusion

The information just presented indicates that *increased lactate production in critically ill patients may be predominantly aerobic in origin*. In fact, anaerobic lactate production is likely to be an uncommon event, as stated in a recent review of this topic (44):

> Today, it is well established that any increase in lactate concentration typically represents something other than O_2 limitation; hypoxia-driven lactate accumulation is very much the exception rather than the rule.

So why is lactate production increased in critical illness? One possible answer is presented next.

Lactate as an Oxidative Fuel

Lactate can be viewed, not as a waste product of anaerobic metabolism, but rather as an alternative fuel source during periods of metabolic stress (39,44). The energy yield from the oxidative metabolism of lactate is equivalent to that of glucose, and this is shown in Table 9.6. The caloric density (kcal/g) of lactate and glucose are equivalent and, since one glucose molecule

produces 2 lactate molecules, the energy yield from the complete oxidation of lactate and glucose are equivalent. Thus, lactate can serve as a source of energy when glucose availability is threatened by heightened metabolic demands.

TABLE 9.6 Glucose vs. Lactate as Oxidative Fuels

Substrate	Molecular Weight (g/mole)	Energy Yield (kcal/mole)	Energy Yield (kcal/g)
Glucose	180	673	3.74
Lactate	90	326	3.62
Lactate x 2	180	652	3.62

In conditions of metabolic stress (such as sepsis), lactate is often used as an oxidative fuel by the heart and brain. In this situation, lactate can provide 60% of the energy needs of the myocardium (44), and there is evidence that lactate improves cardiac performance in circulatory shock (45). Lactate can also provide about 25–30% of the energy needs of the brain in stressful conditions (46). Adaptations like these help to preserve the viability of the heart and brain in life-threatening conditions.

A FINAL WORD

Is Cellular Hypoxia a Common Cause of Death?

Since it is not possible to monitor tissue O_2 levels, the notion that impaired tissue oxygenation is responsible for multiorgan failure and fatal outcomes in critically ill patients is largely based on studies showing a correlation between plasma lactate levels and mortality. However, this interpretation is based on the assumption that lactate elevation is a marker of anaerobic metabolism in critically ill patients, which is likely not the case (as presented in the latter part of this chapter).

There is evidence (from animal studies) that intracellular PO_2 levels are as low as 1 mm Hg (47), and further, that aerobic production of ATP can continue down to PO_2 levels of ≤0.5 mm Hg (33,48). These observations indicate that *there is an oxygen-poor environment in the interior of cells, and that aerobic metabolism is designed to operate in such an environment* (49). As such, cell injury from a low PO_2 seems unlikely. The culprit in multiorgan failure is more likely to be inflammatory cell injury, especially in sepsis/septic shock, which is the leading cause of in-hospital deaths in the United States (40).

So, why is there an oxygen-poor environment in our cells? For the same reason that we store food in vacuum-sealed containers, and wrap our sandwiches in cellophane; i.e., because *oxygen disrupts or decomposes organic (carbon-based) matter*, which includes all of our vital cell components. (See Chapter 25 for more on oxygen-related cell injury.)

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Section IV

INTRAVENOUS FLUID THERAPY

Life is water dancing to the tune of solids.

Albert Szent-Gyorgi

Chapter 10

Intravenous Fluids

The secret of science is to ask the right question …

Sir Henry Tizard (*a*)

The first intravenous fluid was a mixture of opium, wine and beer, which was infused through a goose quill into the vein of a dog. The year was 1656, and the infusion was carried out by a well-known London architect named Christopher Wren (the designer of St. Paul's Cathedral in London). The dog's response to the infusion was stated as follows: *"It made him extremely drunk, but soon after he Pisseth it out"* (1). This rather comical report received little attention, as the dominant approach to illness in the 17th and 18th centuries involved the *removal* of fluid by bloodletting and the use of purgatives. The therapeutic benefit of intravenous fluids was first recognized during the cholera epidemic in the early 19th century, when the infusion of sodium chloride solutions had some success in improving outcomes (2). Thereafter, intravenous fluids gained in popularity for the rehydration of patients with gastroenteritis, but it wasn't until the 1940s, with the advent of blood fractionation and the violence of World War II, that intravenous fluid therapy emerged as a staple of circulatory resuscitation.

Simply stated, the care of critically ill patients would not be possible without the use of asanguinous intravenous fluids, which are classified as crystalloid or colloid fluids based on their tendency to pass through capillary walls. This chapter describes the salient features of these fluids, both individually and as a group.

SOME BASICS

Body Water Distribution

The distribution of fluid in the adult human body is summarized in the following statements.

. Total body water (TBW) accounts for about 60% of the lean body weight (600 mL/kg) in adult males, and 50% of the lean body weight (500 mL/kg) in adult females.

. About two-thirds (≈65 %) of the TBW is located intracellularly, and the remaining one-third (≈35%) is in the extracellular fluid compartment.

. Plasma represents only one-fifth (20%) of the extracellular fluid, and the remaining 80% is located in the interstitial space (discounting the small volumes allotted to cerebrospinal fluid and pleural fluid).

The above information is included in Table 10.1, along with representative body fluid volumes for an average-sized adult male and female. Note the small volume of plasma, which represents only 6−7% of the total body fluid. This is relevant because the goal of intravenous fluid therapy is to support the plasma volume.

TABLE 10.1 Body Fluid Volumes in Adults

Parameter	Derivation	Male	Female
Lean Body Weight		75 kg*	60 kg*
Total Body Water	0.6 x LBW (M) 0.5 x LBW (F)	45 L	30 L
Intracellular Volume	0.65 x TBW	29 L	20 L
Extacellular Volume	0.35 x TBW	16 L	10 L
Interstitial Volume	0.8 x ECV	13 L	8 L
Plasma Volume	0.2 x ECV	3 L	2 L

* Representative weight for an average-sized adult. LBW = lean body weight, TBW = total body water, ECV = extracellular volume.

Osmotic Forces

(*Note:* For a more detailed description of this topic, see the first section of Chapter 35.)
The distribution of water in the intracellular and extracellular fluid compartments is determined by the relative osmotic activity in each compartment; i.e., the compartment with the higher osmotic activity will draw water from the one with the lower osmotic activity. (Relative osmotic activity is often expressed as *tonicity*.) Osmotic activity is determined by the number of solute particles in a solution, and not by the size, electrical charge, or chemical behavior of the solutes. *Sodium is the most abundant solute in the extracellular fluid, and is thus the principal determinant of extracellular fluid volume*. Osmotic activity can be expressed as *osmolarity* (osmotic activity per unit volume of solution) or *osmolality* (osmotic activity per unit volume of water). Extracellular fluid (plasma) is 93% water, so osmolarity and osmolality are often used interchangeably.

Colloid Osmotic Pressure

The distribution of water between the intravascular and extravascular compartment is influenced by the osmotic activity of large molecules in plasma that do not pass freely across the vascular endothelium. Plasma proteins are the principal source of this osmotic activity, which acts to hold water in the intravascular compartment. The osmotic force generated by large, semipermeable or impermeable molecules is called the *colloid osmotic pressure*, or the oncotic pressure. *Albumin is the most abundant plasma protein, and is the principal source of the colloid osmotic pressure*

in plasma.

CRYSTALLOID FLUIDS

Crystalloid fluids are aqueous solutions that contain small molecules (mostly electrolytes) that diffuse freely from intravascular to interstitial fluid compartments. The principal component of crystalloid fluids is sodium chloride.

Normal Saline

The most frequently used crystalloid fluid is 0.9% sodium chloride (0.9% saline), with annual sales of 200 *million* liters in the United States (data from Baxter Healthcare). The popular name for this solution is *normal saline*, which is attributed to a Dutch chemist named Hartog Hamburger, who studied the freezing point depression of plasma in the late 19th century, and concluded incorrectly that plasma is a 0.9% salt solution (3). (Human plasma is actually a 0.6% salt solution.) A more appropriate name for 0.9% saline is *isotonic saline*, but even this name is not accurate (see next).

Normal Saline is NOT Normal

Normal saline (0.9% saline) is not chemically normal because a one-normal (1 N) NaCL solution contains 58 grams of NaCL per liter (the combined molecular weights of sodium and chloride), while a 0.9% NaCL solution contains only 9 grams of NaCL per liter. It is also not physiologically normal because 0.9% saline has several features that differ from plasma. These are shown in Table 10.2. When compared to plasma, 0.9% saline has a higher sodium concentration (154 vs. 140 mEq/L), a much higher chloride concentration (154 vs. 103 mEq/L), a higher osmolality (308 vs. 290 ± 5 mOsm/L), and a lower pH (5.7 vs. 7.4). The difference in chloride concentration is most relevant, as described later.

TABLE 10.2 Crystalloid Fluids in Relation to Plasma

Fluid	mEq/L							Omolarity (mOsm/L)
	Na	CL	K	Ca*	Mg*	Buffers	pH	
Plasma	140	103	4	2	3	HCO_3^- (25)	7.4	290
0.9% NaCL	154	154	–	–	–	–	5.7	308
Ringer's Lactate	130	109	4	3	–	Lactate (28)	6.5	273
Ringer's Acetate	131	109	4	3	–	Acetate (28)	6.7	275
Normosol®	140	98	5	–	3	Acetate (27)	7.4	295
Plasma-Lyte®						Gluconate (23)		

*Concentration of ionized calcium and total magnesium in mEq/L.
Plasma components are average or median values. Buffer concentrations in parentheses.

Volume Effects

The sodium in crystalloid fluids distributes uniformly in the extracellular fluid. Because plasma represents only 20% of the extracellular fluid, *the predominant effect of 0.9% saline infusions is to expand the interstitial volume, not the plasma volume*. This is demonstrated in Figure 10.1, which shows that infusion of one liter of 0.9% saline adds 825 mL to the interstitial volume and only 275 mL to the plasma volume (4). Note that the total increase in extracellular volume (1,100 mL) is slightly greater than the infused volume. This is due to 0.9% saline being slightly hypertonic to the extracellular fluid, which prompts a shift in water from intracellular to extracellular fluid.

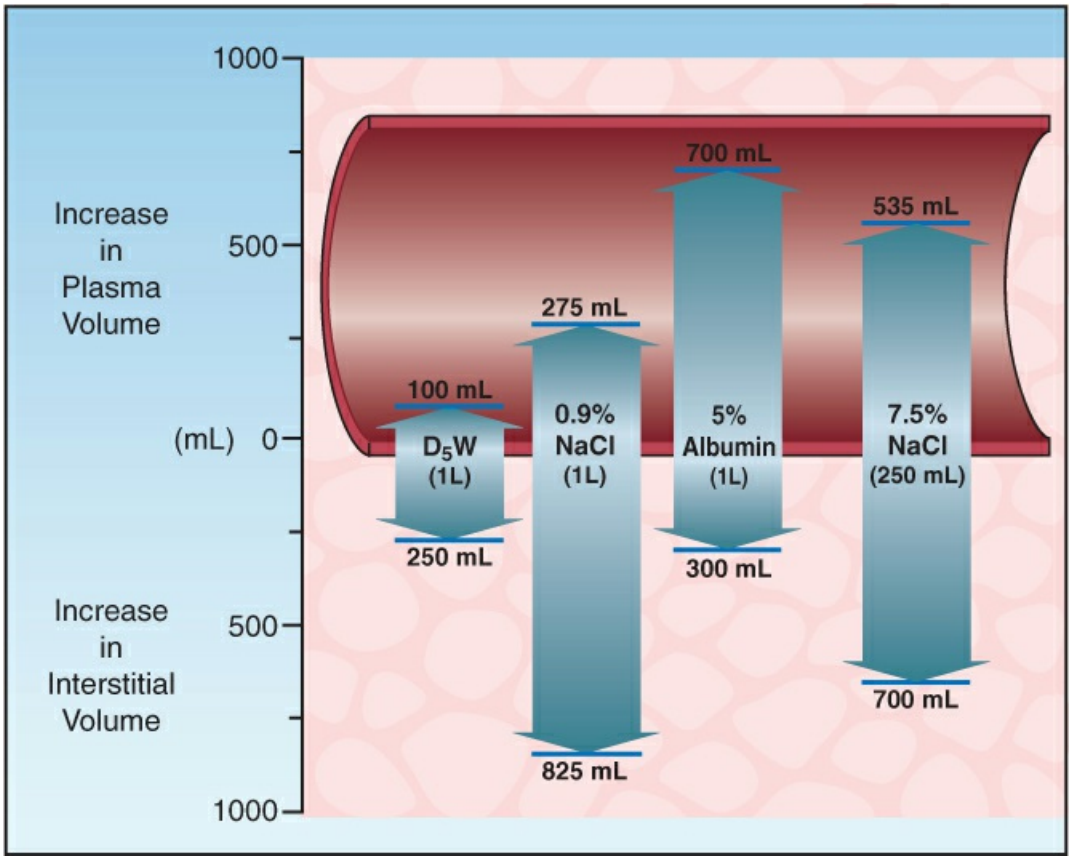

FIGURE 10.1 The effect of crystalloid and colloid fluids on expanding the plasma and interstitial fluid volumes. The infusion volume of each fluid is shown in parentheses. Data from Reference 4.

All crystalloid fluids suffer from the tendency to promote edema formation, but this tendency may be greater with 0.9% saline because of its higher sodium content (as illustrated in Figure 10.1). In addition, 0.9% saline has been implicated as a cause of acute kidney injury (see later), which will promote sodium accumulation and aggravate the tendency for edema formation.

The Evils of Chloride

There are two adverse effects of 0.9% saline that are related to the high concentration of chloride in the solution. The first of these is a *hyperchloremic metabolic acidosis*, which is the most cited adverse consequence of isotonic (0.9%) saline infusions, and usually occurs with rapid or prolonged infusions (5,6). This effect is demonstrated in Figure 10.2, which is from a study of high-volume infusions during gynecological surgery (6). The isotonic saline infusion was accompanied by a progressive decline in the blood pH (from 7.41 to 7.28), while the pH was unchanged during an equivalent infusion of Ringer's lactate solution, which has a much lower chloride concentration than isotonic saline (109 vs. 154 mEq/L), and also contains lactate as a buffer. The tendency of 0.9% saline to produce a metabolic acidosis has led to a decline in its popularity as a resuscitation fluid, especially in conditions like diabetic ketoacidosis (7).

Infusions of 0.9% saline have also been associated with *impaired renal function*, which is attributed to chloride-mediated renal vasoconstriction (5,8). Studies employing a chloride-restrictive fluid strategy (e.g., with Ringer's lactate or Plasma-Lyte) have shown a lower

incidence of acute kidney injury (AKI) when compared with a chloride-liberal strategy using 0.9% saline (9,10). However, the AKI associated with 0.9% saline is typically mild in severity, and does not require renal replacement therapy (11).

Ringer's Lactate

The family of Ringer's solutions began with Sydney Ringer, a British physician who studied the contraction of isolated frog hearts, and who (in 1880) introduced a saline solution that contained calcium and potassium to promote cardiac contraction and cell viability (12). This solution, which is known as *Ringer's injection*, is 0.9% saline with potassium at 4 mEq/L, and calcium at 4 mg/dL.

The original Ringer's solution was modified in the early 1930's by an American pediatrician named Alexis Hartmann, who added sodium lactate as a buffer for the treatment of metabolic acidosis (12). This solution was originally called Hartmann's solution, and is now known as *Ringer's lactate* (RL) solution. The composition of this solution is shown in Table 10.2. The sodium concentration in RL is reduced to compensate for the sodium released from sodium lactate, and the chloride concentration is reduced to adjust for the lactate anion in the solution. Note that the chloride concentration in RL (109 mEq/L) is a close approximation of the chloride in plasma (103 mEq/L); as a result, RL infusions do not produce a hyperchloremic metabolic acidosis, as demonstrated in Figure 10.2.

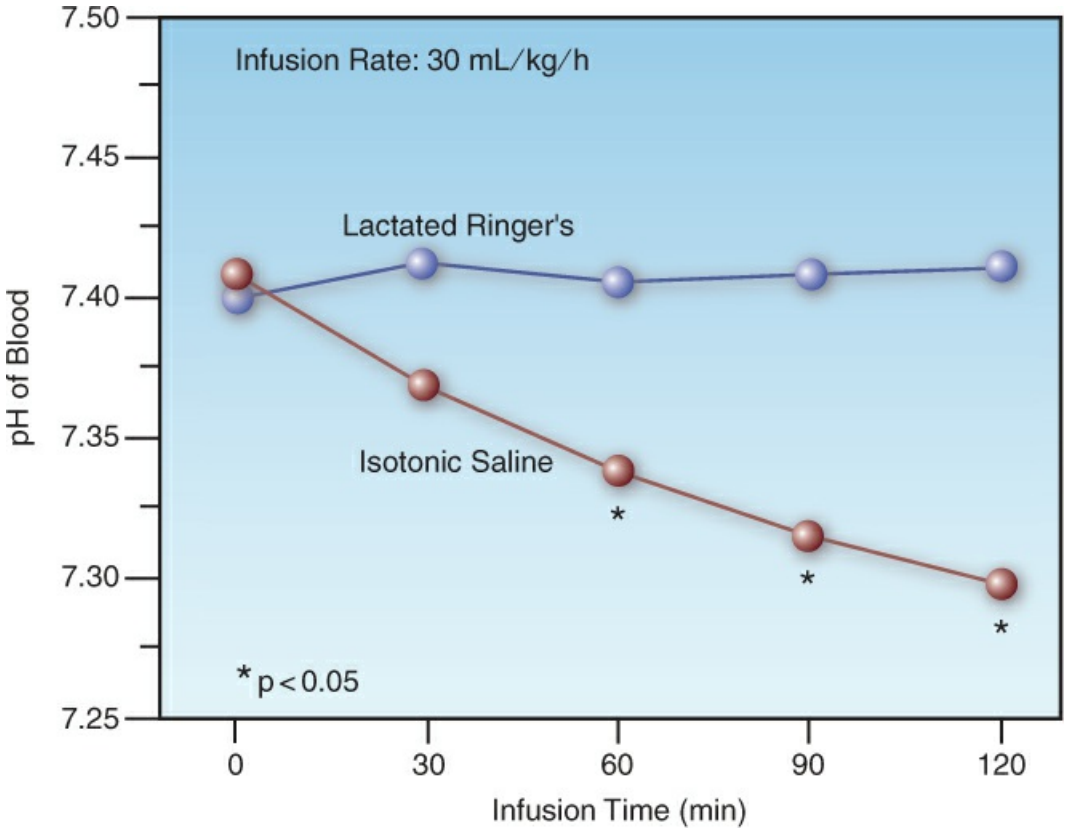

FIGURE 10.2 Cumulative effects of isotonic saline (CL = 154 mEq/L) and Ringer's lactate (CL = 109 mEq/L) on the pH of blood. Both fluids were infused at the same rate (30 mL/kg/hr). Data from Reference 6.

Lactate as a Buffer

The lactate anion in RL can serve as a buffer, but not by combining with hydrogen ions in blood. Instead, the lactate is taken up by the liver and converted to glucose, which consumes hydrogen ions (13): i.e.,

$$2\ \text{Lactate} + 2H^{+} \rightarrow \text{Glucose} \tag{10.1}$$

The hydrogen ions are donated by water, which leaves hydroxyl ions (OH-) that can combine with CO_2 to generate bicarbonate ions (HCO_3^-):

$$2\ OH^{-} + 2\ CO_2 \rightarrow 2\ HCO_3^{-} \tag{10.2}$$

Overall, each mmol of lactate generates one mmol of bicarbonate (13).

Plasma Lactate Levels

Concern about the lactate in RL (28 mmol/L) causing an increase in plasma lactate levels has received scant attention. The liver can normally clear lactate at a rate of 100 mmol/hr (14), which is equivalent to the infusion of 3.5 liters of RL per hour. In one study of healthy adult volunteers, the bolus infusion of RL at a dose of 30 mL/kg resulted in a small (0.9 mmol/L) increase in plasma lactate levels, but isotonic saline infusions had a similar effect (15). The influence of RL infusions on lactate levels in critically ill patients, who may have impaired lactate clearance from circulatory shock or hepatic insufficiency, has not been studied.

Caveat: Blood samples drawn through catheters being used for RL infusions can yield spuriously high lactate concentrations (16). Therefore, in patients receiving RL infusions, plasma lactate measurements should be obtained from sites other than the infusion catheter.

Other Issues

Other issues related to RL infusions are summarized as follows:

. The ionized calcium in RL can bind to the citrated anticoagulant in stored RBCs and promote clot formation; as a result, RL is not advised as a diluent fluid for the transfusion of erythrocyte concentrates (packed RBCs). This recommendation lacks experimental support, and there are studies showing that *rapid* infusion of RBCs and RL is safe (17). However, it still seems best to avoid RL for RBC transfusions if possible.

. The potassium in RL (4 mEq/L) is not a concern in patients with hyperkalemia, as there are no documented instances in which hyperkalemia is exacerbated by RL (18). In fact, hyperkalemia is more likely with 0.9% saline (due to the metabolic acidosis described earlier) than with RL (19).

Ringer's Acetate

Because of concerns that the lactate buffer in RL would be ineffective in patients with liver disease, and would also elevate plasma lactate levels, lactate was replaced by acetate to create *Ringer's acetate* solution (see Table 10.2), which is otherwise identical in composition to RL. Acetate is metabolized primarily in muscle (12), which makes Ringer's acetate a reasonable alternative to RL in patients with liver failure. One potential disadvantage of acetate is the

potential for myocardial depression (5), although the clinical significance of this is unclear.

Other Balanced Salt Solutions

Normosol® and Plasma-Lyte® are balanced salt solutions that are identical in composition (see Table 10.2), and offer the following advantages:

. They have a pH that is closer to plasma pH than other crystalloid fluids.

. They contain non-lactate buffers, which eliminates the combined risks of altered buffer capacity in liver failure and spurious hyperlactatemia.

. The chloride concentration is close to that of plasma, and will not produce a hyperchloremic metabolic acidosis.

. They contain magnesium instead of calcium, and thus are safe to use with blood transfusions.

. They are more isotonic to plasma than other crystalloid fluids.

In terms of their general characteristics, these fluids are closest to the ideal plasma replacement fluid. However, their superiority in clinical settings is unproven.

Hypertonic Saline

Hypertonic saline solutions are much more effective at expanding the extracellular (plasma) volume than isotonic fluids. This is demonstrated in Figure 10.1, which shows that infusion of 250 mL of 7.5% NaCL (which has an osmolarity of 2,567 mOsm/L; 9 times that of plasma) results in a 1,235 mL increase in extracellular fluid, which is about 5 times greater than the infused volume. The added volume comes from an intracellular shift of water.

Animal studies have shown that hypertonic saline is effective for limited-volume resuscitation of hemorrhagic shock. This is demonstrated in Figure 10.3, which shows that hypertonic saline can maintain cardiac output with 1/5th the volume required with isotonic saline (20). Observations like this suggested that hypertonic saline would be well suited for situations where small volumes of resuscitation fluid are advantageous; e.g., the prehospital resuscitation of trauma victims. However, the accumulated evidence shows no apparent survival benefit from hypertonic saline compared to isotonic crystalloids for the management of traumatic shock (21).

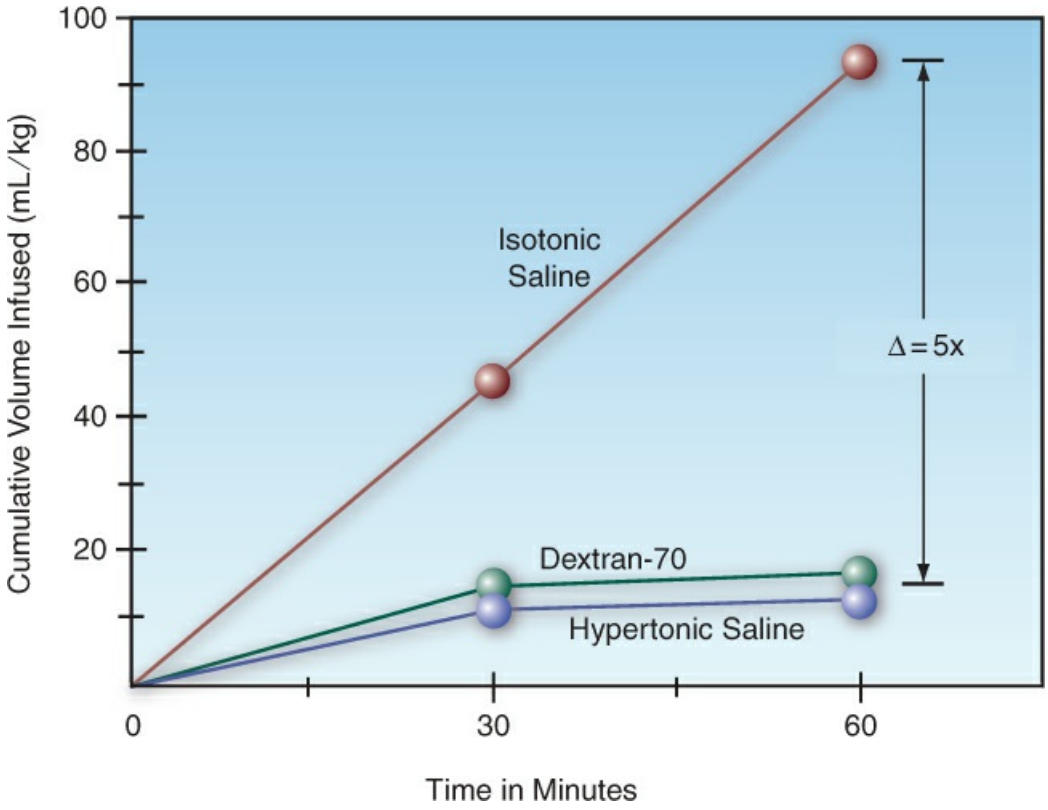

FIGURE 10.3 The cumulative volume of three intravenous fluids needed to maintain a normal rate of aortic blood flow in an animal model of hemorrhagic shock. Data from Reference 20.

Traumatic Brain Injury

The principle use of hypertonic saline is to reduce intracranial pressure (ICP) in patients with traumatic brain injury. The standard agent for this is mannitol (a 6-carbon sugar-alcohol that is also used as an osmotic diuretic), but hypertonic saline is gaining in popularity because it is equivalent to mannitol for reducing ICP, but is more likely to maintain cerebral perfusion pressure (22). Hypertonic saline also avoids the risk of acute kidney injury that has been linked to mannitol.

The saline solutions used for ICP control vary in strength from 3% to 25% saline, but 10% saline is a popular choice, and a dose of 0.6 mL/kg is equimolar to 20% mannitol at 2 mL/kg (23). Bolus doses are given every 6–8 hours as needed to keep ICP <20 mm Hg, and treatment can be continued as long as the serum osmolality is <320 mmol/kg H_2O. Unfortunately, control of ICP with hypertonic saline or mannitol has not improved the survival rate in patients with traumatic brain injury (24).

5% DEXTROSE SOLUTIONS

The once-popular use of 5% dextrose solutions (D_5 solutions) is no longer a desirable option, as explained in this section.

Protein-Sparing Effect

Prior to the standard use of nutritional support regimens (e.g., enteral tube feedings), 5% dextrose solutions were used as a source of calories in patients who were unable to eat. Dextrose provides 3.4 kilocalories (kcal) per gram when fully metabolized, so a 5% dextrose solution (50 grams dextrose per liter) provides 170 kcal per liter. Infusion of 3 liters of a D_5 solution daily (125 mL/min) will then provide 510 kcal/day, which is enough nonprotein calories to limit the breakdown of endogenous proteins to provide calories (protein-sparing effect). This is no longer necessary, as most patients who are unable to eat will receive full nutritional support (enteral or parenteral) when needed.

Volume Effects

The addition of dextrose to intravenous fluids increases osmolarity; a 5% dextrose-in-water solution (D_5W) has an osmolarity of 278 mOsm/L, which is close to the osmolarity of plasma. However, since the dextrose is taken up by cells and metabolized, the osmotic effect rapidly wanes, and the added water then moves into cells. This explains the volume effects of D_5W shown in Figure 10.1; i.e., infusion of one liter of D_5W results in an increase in extracellular fluid (plasma plus interstitial fluid) of about 350 mL, which means the remaining 650 mL (two-thirds of the infused volume) has moved intracellularly. Thus, *the principal effect of D_5W is to expand the intracellular, not extracellular volume*, and this can result in undesirable cell swelling.

A very different effect can occur when dextrose is added to isotonic (“normal”) saline. A solution of D_5-normal saline (D_5NS) has an osmolarity of 560 mOsm/L, which is almost twice the osmolarity of plasma. Therefore, *if glucose utilization is impaired* (which is common in critically ill patients), *infusions of D_5NS can result in cellular dehydration*.

Enhanced Lactate Production

In healthy subjects, only 5% of an infused glucose load will result in lactate formation, but in patients who are hemodynamically compromised, as much as 85% of glucose metabolism can lead to lactate production (25). This latter effect is demonstrated in Figure 10.4, which is from a study where two intravenous fluids were used (Ringer’s solution and a 5% dextrose solution) to maintain cardiac filling pressures during a surgical procedure in which systemic hypoperfusion was induced by aortic cross-clamping (26). When the dextrose-containing fluid was infused, the serum lactate levels began to rise significantly after the aorta was cross-clamped, and the increase in circulating lactate levels persisted throughout the remainder of the procedure. These results indicate that, *when circulatory flow is compromised, infusion of 5% dextrose solutions can promote lactic acid production*.

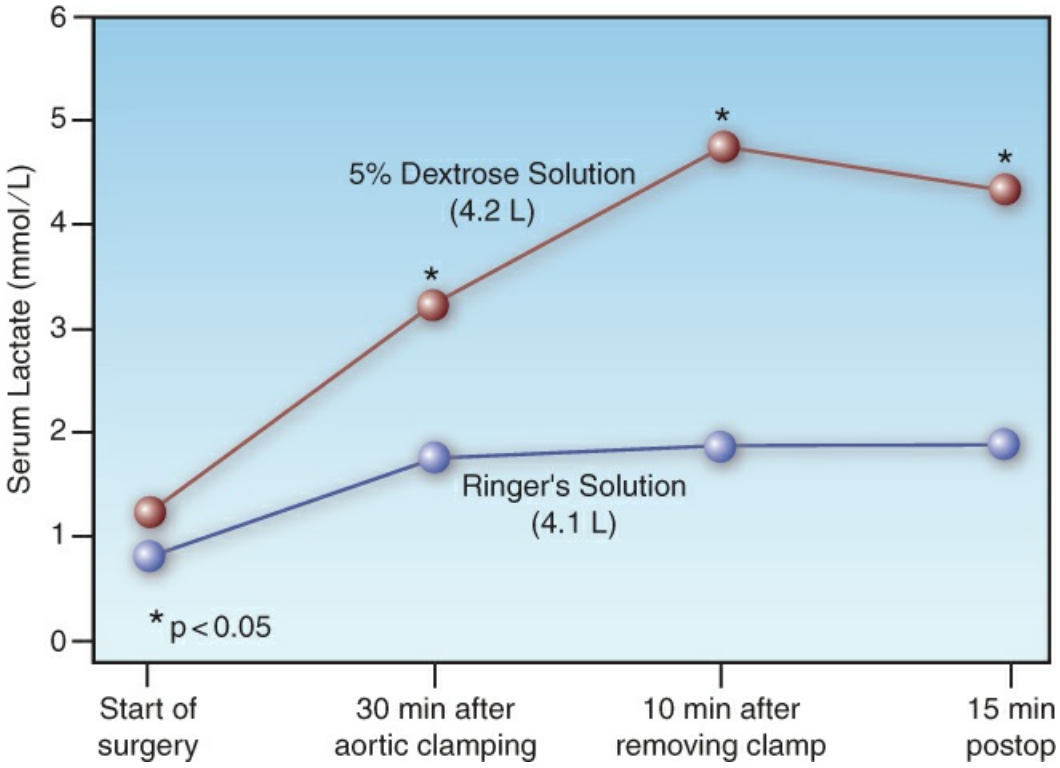

FIGURE 10.4 The effect of intravenous fluid therapy with and without dextrose on blood lactate levels in patients undergoing abdominal aortic aneurysm repair. Each point represents the mean lactate level in 10 study patients. The average infusion volume for each fluid is indicated in parentheses. Data from Reference 26.

Hyperglycemia

About 20% of patients admitted to ICUs have diabetes, and as many as 90% of patients develop hyperglycemia at some time during their ICU stay (27). Hyperglycemia has several deleterious consequences in critically ill patients, including immune suppression and increased risk of infection (28), aggravation of ischemic brain injury (29), and an increased mortality rate (27). Considering the ubiquity of hyperglycemia and the associated risks, it seems reasonable to *avoid using dextrose-containing fluids whenever possible*.

COLLOID FLUIDS

In chemical terms, a colloidal solution (also called a "suspension") is a fluid that contains insoluble particles. In clinical terms, a colloid solution is a fluid that contains large solute molecules that do not pass readily from plasma to interstitial fluid. The retained molecules create a *colloid osmotic pressure* or *oncotic pressure* (described earlier in the chapter), which holds water in the vascular compartment.

Volume Effects

The effect of volume resuscitation with a colloid fluid is demonstrated in Figure 10.1. The colloid fluid in this case is a 5% albumin solution. Infusion of one liter of this solution results in

a 700 mL increment in the plasma volume and a 300 mL increment in the interstitial fluid volume. When compared with the increment in plasma volume after one liter of 0.9% NaCL (275 mL), the colloid fluid is about 3 times more effective in expanding the plasma volume than the crystalloid fluid. Thus, *colloid fluids will achieve a given increment in plasma volume with about 30% of the volume required with crystalloid fluids* (30).

TABLE 10.3 Colloid Fluid Comparisons

Fluid	COP (mm Hg)	Δ Plasma Volume / Infusate Volume	Duration of Effect
25% Albumin	70	3.0−4.0	12 h
10% Dextran-40	40	1.0−1.5	6 h
6% Hetastarch	30	1.0−1.3	24 h
5% Albumin	20	0.7−1.3	24 h
Plasma	28	–	–

Data from References 4,31–34. COP = colloid osmotic pressure.

Colloid Fluid Comparisons

Individual colloid fluids differ in their ability to expand the plasma volume, and this difference is a function of the colloid osmotic pressure (COP) of each fluid, and its relation to the COP of plasma (which is normally about 28 mm Hg) (31). This is demonstrated in Table 10.3, which shows the COP of common colloid fluids and the potency of each as a plasma volume expander (4,31−34). Note that fluids with higher COPs produce greater increments in plasma volume, and when the COP exceeds that of plasma, the increment in plasma volume exceeds the infusate volume. This latter point is most apparent with 25% albumin, which has a COP of 70 mm Hg (2.5 times the plasma COP), and produces an increment in plasma volume that is 3 to 4 times greater than the infusate volume.

Albumin Solutions

Albumin is responsible for about 80% of the plasma COP (31), which makes albumin solutions very desirable as plasma volume expanders. Added benefits of albumin include its role as the principal transport protein in the blood (see Table 10.4), and its antioxidant activity (35).

Characteristics

Albumin solutions are heat-treated preparations of human serum albumin that are available as a 5% solution (5 g/100 mL) and a 25% solution (25 g/mL) in 0.9% NaCL. The 5% albumin solution has a COP of 20 mm Hg, which is close to the COP of plasma. It is typically given in aliquots of 250 mL, and the plasma volume increment is at least 70% of the infused volume. The volume effect begins to dissipate at 6 hours, and is usually lost after 12 hours (4,32).

TABLE 10.4 Substances Transported by Albumin

Drugs	Others
Benzodiazepines	Bilirubin
Cephalosporins	Copper
Furosemide	Estrogen
NSAIDs	Fatty Acids
Phenytoin	Progesterone
Quinidine	Prostaglandins
Salicylates	Testosterone
Sulfonamides	Zinc
Valproic Acid	
Warfarin	

The 25% albumin solution is a hyperoncotic fluid with a COP that is 2.5 times greater than that of plasma. It is given in aliquots of 50–100 mL, and the plasma volume increment is 3 to 4 times the infusate volume. This effect is produced by fluid shifts from the interstitial space, so interstitial fluid volume decreases as plasma volume increases. Because it does not replace lost volume, but instead shifts fluid from one compartment to another, *25% albumin should not be used as a resuscitation fluid for volume loss*. This fluid is typically used to promote a rapid increase in plasma volume (and blood pressure) in patients with edema, especially when the edema is due, at least in part to hypoalbuminemia. All *albumin solutions are more effective as plasma volume expanders in the presence of hypoalbuminemia* (36).

Safety

Early reviews suggested that the use of albumin solutions had a negative impact on survival (37), but more recent studies show that albumin solutions pose no danger (38,39). One possible exception is traumatic brain injury, where one large study has shown a higher mortality associated with albumin resuscitation when compared with isotonic saline (40). Hyperoncotic (25%) albumin has been associated with an increased risk of renal impairment in patients with circulatory shock, but this risk is shared by all hyperoncotic fluids (41).

Hydroxyethyl Starches

Hydroxyethyl starch (HES) is a chemically modified polysaccharide composed of long chains of branched glucose polymers substituted periodically by hydroxyl radicals (OH), which resist enzymatic degradation. HES elimination involves hydrolysis by amylase enzymes in the bloodstream, which cleave the parent molecule until it is small enough to be cleared by the kidneys. The following is a summary of the relevant characteristics of HES preparations (34,42).

Characteristics

MOLECULAR WEIGHT: HES preparations have different molecular weights, and are classified as high MW (450 kilodaltons or kD), medium MW (200 kD) and low MW (70 kD). High MW preparations have a prolonged duration of action because amylase cleavage results in progressively smaller molecules that are osmotically active. When the cleavage products reach a molecular weight of 50 kD, they can be cleared by the kidneys (42).

MOLAR SUBSTITUTION RATIO: HES preparations are also classified by the ratio of hydroxyl radical substitutions per glucose polymer (OH/glucose), which is called the *molar substitution ratio* and ranges from zero to one (42). The molar substitution ratio identifies the type of starch in the HES preparation; e.g., 0.7 is hetastarch, 0.4 is tetrastarch. Because hydroxyl radicals resist enzymatic degradation, higher OH/glucose ratios are associated with prolonged activity. However, higher molar substitution ratios also increase the risk of adverse effects (see later).

HES PREPARATIONS: Individual HES preparations are described by their concentration, MW, and molar substitution ratio, as shown in Table 10.5. Most preparations are available as a 6% solution in 0.9% NaCL, and the molar substitution ratio is indicated in the prefix of the starch: e.g., 0.5 is pentastarch, 0.4 is tetrastarch. Hetastarch is the original HES preparation, and has a high MW(450 kD) and a high molar substitution ratio (0.7). Tetrastarch is the most recent HES preparation, and has the lowest MW (130 kD) and the lowest molar substitution ratio (0.4). Tetrastarch is available as Voluven® (6% HES 130/0.4 in 0.9% saline).

TABLE 10.5 Characteristics of Hydroxyethyl Starch Preparations

Name	Concentration	MW	MSR
Hetastarch	6%	450 kD	0.7
Hexastarch	6%	200 kD	0.6
Pentastarch	6%, 10%	200 kD	0.5
Tetrastarch	6%	130 kD	0.4

Volume Effects

The performance of 6% HES solutions as plasma volume expanders is very similar to 5% albumin. The oncotic pressure is higher than 5% albumin, and the increment in plasma volume can be higher as well (see Table 10.3). The effect on plasma volume can last up to 24 hours with high MW preparations (e.g., hetastarch) (34), while the effect with lower MW preparations (tetrastarch) can be 6 hours or even less (43).

Altered Hemostasis

HES preparations can impair hemostasis by inhibition of Factor VII and von Willebrand factor, and impaired platelet adhesiveness (42,44). The risk of altered hemostasis is highest with HES preparations that have a high molar substitution ratio (i.e., hetastarch) (42), and clinical studies have shown an increase in perioperative bleeding and transfusion requirements when hetastarch is used for volume resuscitation (45). There is evidence that tetrastarch (which has a low molar substitution ratio) does not produce a clinically significant coagulopathy until large volumes are infused (>50 mL/kg) (27).

Nephrotoxicity

Several clinical studies have shown an association between HES infusions and an increased risk of acute kidney injury (AKI) and death (46,47). However, many of these studies used an older-

generation HES preparation (e.g., hetastarch), and the patients often had circulatory shock, which increases the risk of AKI. In more recent studies using the latest generation HES preparation (tetrastarch) in less severely ill (abdominal surgery) patients, there is no association between HES infusions and AKI (48). At the present time, the risk of AKI with HES infusions is an unresolved issue (49).

Hyperamylasemia

The amylase enzymes involved in the hydrolysis of HES attach to the HES molecules, and this reduces amylase clearance by the kidneys. This can result is an increase in serum amylase levels to 2–3 times normal (34,50). Levels usually return to normal within one week after HES is discontinued. Serum lipase levels are unaffected by HES infusions (50).

The Dextrans

The dextrans are glucose polymers produced by a bacterium (*Leuconostoc*) incubated in a sucrose medium. First introduced in the 1940s, these colloids are not popular (at least in the United States) because of the perceived risk of adverse reactions. The two most common dextran preparations are 10% dextran-40 and 6% dextran-70, which have average molecular weights of 40 and 70, respectively.

Characteristics

Both dextran preparations have a COP of 40 mm Hg, and cause a greater increase in plasma volume than either 5% albumin or 6% hetastarch (see Table 10.3). Dextran-70 may be preferred because the duration of action (12 hours) is longer than that of dextran-40 (6 hours) (32).

Disadvantages

. Dextrans produce a dose-related bleeding tendency that involves impaired platelet aggregation, decreased levels of Factor VIII and von Willebrand factor, and enhanced fibrinolysis (44,50). The hemostatic defects are minimized by limiting the daily dextran dose to 20 mL/kg.

. Dextrans coat the surface of red blood cells and can interfere with the ability to cross-match blood. Red cell preparations must be washed to eliminate this problem. Dextrans also increase the erythrocyte sedimentation rate as a result of their interactions with red blood cells (50).

. Dextrans have been associated with a hyperoncotic renal injury (50,51), but this occurs rarely. Anaphylactic reactions are reported in only 0.03% of infusions (50).

THE COLLOID–CRYSTALLOID CONUNDRUM

There is a longstanding debate concerning the type of fluid that is most appropriate for volume resuscitation, and each type of fluid has its loyalists who passionately defend the merits of their chosen fluid. The following is a brief description of the issues involved in this debate.

Early Focus on Crystalloids

Early studies of acute blood loss showed that hemorrhagic shock was associated with an

interstitial fluid deficit, partly as a result of a fluid shift from the interstitial fluid into the bloodstream (52). Studies in an animal model of hemorrhagic shock showed that replacement of the shed blood was almost universally fatal, while the mortality rate was reduced when a crystalloid fluid (Ringer's lactate) was added to the shed blood replacement (53). These results were interpreted as indicating that replacement of the interstitial fluid deficit (with a crystalloid fluid) was the critical factor in the successful resuscitation of hemorrhagic shock. This cemented the popularity of crystalloid fluids for the resuscitation of blood loss.

Current Concerns

Since those early studies, the importance of promoting cardiac output has emerged as the primary focus of volume resuscitation. To this end, colloid fluids have proven far superior to crystalloid fluids for producing acute increments in cardiac output: in one study, 500 mL of a colloid fluid (10% Dextran-40) produced a three-fold greater increment in cardiac output than one liter of a crystalloid fluid (Ringer's lactate) (54). This superiority is a reflection of the greater plasma volume expansion with colloid fluids.

Despite the enhanced ability of colloid fluids to promote cardiac output, crystalloid fluids remain the popular choice for volume resuscitation in circulatory shock. The principal argument in favor of crystalloid resuscitation is the lack of proven survival benefit with colloid resuscitation (55), and the lower cost of crystalloid fluids. The argument against crystalloid resuscitation is the relatively large volumes needed to expand the plasma volume (at least 3 times greater than the volume of colloid fluids), and the attendant risk of fluid accumulation and edema formation, which is associated with increased morbidity and mortality (56).

A Tailored Approach

The colloid-crystalloid controversy is focused on selecting one type of fluid for all clinical situations. This seems unreasonable considering the multitude of clinical scenarios encountered in critically ill patients. A more reasonable approach would be to select a fluid that is most appropriate for a specific clinical condition. The following are three clinical situations where a different resuscitation fluid would be most effective.

. In cases of life-threatening hypovolemia (where prompt restoration of the plasma volume is desirable), colloid fluid resuscitation (e.g., with 5% albumin) would be most effective.

. In cases of hypovolemia due to dehydration (where there is a uniform loss of extracellular fluid), a crystalloid fluid (e.g., Ringer's lactate) is appropriate.

. In cases of hypovolemia where hypoalbuminemia is implicated (causing fluid shifts from plasma to interstitial fluid) a hyperoncotic colloid fluid (e.g., 25% albumin) is an appropriate choice.

As demonstrated in these examples, *tailoring the type of resuscitation fluid to the specific clinical condition is a more logical approach than using the same type of fluid for all cases of hypovolemia*. This approach is "asking the right question", so it should qualify as a scientific approach.

A FINAL WORD

The following information in this chapter merits emphasis:

. Normal saline (0.9% NaCL) is not normal, chemically or physiologically, and the high chloride concentration causes a hyperchloremic metabolic acidosis. This does not occur with more balanced crystalloid fluids (e.g., Ringer's lactate).

. Isotonic crystalloid fluids expand the interstitial fluid volume more than the plasma volume. Thus, they promote fluid accumulation and edema formation, which has deleterious consequences in critically ill patients. (This topic is the focus of the next chapter).

. Dextrose-containing fluids promote lactate formation and hyperglycemia in critically ill patients, and are ill-advised for routine use.

. Colloid fluids are superior to crystalloid fluids for expanding the plasma volume and promoting cardiac output.

. Albumin solutions not only expand the plasma volume, they also support the transport function and antioxidant activity of plasma albumin.

. The hydroxyethyl starch (HES) solutions are associated with an increased risk of bleeding and renal impairment, but the newest generation of HES solutions (i.e., tetrastarch) have a lower risk of toxicity, especially when used in patients who are not critically ill (e.g., postop patients).

. The colloid-crystalloid controversy is misguided because there is no single type of fluid that is optimal for all cases of hypovolemia.

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Chapter 11

Fluid Management

Restoration to normal physiology and normal function of organs … can never be achieved by inundation.

Francis Moore & G. Thomas Shires (*a*)

Humans can survive for several weeks without food, but they will succumb after just a few days without water. This need for water explains (teleologically) why the physiological response to stress or injury involves the retention of water by the kidneys (via the actions of antidiuretic hormone released from the posterior pituitary). The goal, of course, is to support cardiac output and maintain tissue perfusion. Intravenous fluid therapy has the same intent, however the infusion of fluids in critically ill patients is often excessive, especially in patients who are hemodynamically unstable, and the resulting fluid overload has a well-documented negative impact on both morbidity and mortality (1).

The frequency and deleterious consequences of iatrogenic fluid overload has led to a renewed focus on fluid management in the ICU, to identify and correct the practices that promote fluid overload (2). This chapter has a similar focus, and includes sections on the physiology of fluid resuscitation, current problems with infusion therapy, markers of tissue hypoperfusion, and the evaluation of fluid responsiveness.

VENOUS RETURN

Volume resuscitation is aimed at promoting venous return to the heart, and a misunderstanding of the physiology of venous return can result in the inappropriate use of intravenous fluids.

Determinants of Venous Return

The pressure gradient for venous return is often assumed to be the difference between the mean arterial pressure and the pressure in the right atrium, but this is not the case. An explanation for this is provided by the illustration in Figure 11.1, which shows a large sink that is filled with water, and a spigot that is adding water from an upper tank. The lower sink in this case represents the venous system (which contains 75% of the blood volume), and the upper tank represents the arterial side of the circulation. The flow of water out of the lower sink (i.e., venous

return) is driven by the hydrostatic pressure exerted by the height of the water in the sink, and not by the pressure in the upper tank (i.e., the arterial pressure). Thus, *the driving pressure for venous return is distinct from the arterial pressure* (3).

The pressure gradient that drives venous return (ΔPv) is the pressure drop from the small veins or venules to the right atrium. The upstream pressure in the small veins or venules is known as the *mean systemic pressure* (PMS), and *is equivalent to the pressure in the systemic circulation in the absence of blood flow* (4,5). Venous return can then be described as follows:

$$\text{Venous Return} = (\text{Pms} - \text{PRA})/\text{Rv} \tag{11.1}$$

where Pms is the mean systemic pressure, PRA is the right atrial pressure, and Rv is the resistance to flow in the venous circulation. Since the central venous pressure (CVP) is the clinical measure of right atrial pressure, Equation 11.1 can be rewritten as:

$$\text{Venous Return} = (\text{Pms} - \text{CVP})/\text{Rv} \tag{11.2}$$

Volume resuscitation has little impact on Rv (6), so *the goal of fluid resuscitation should be an increase in the (Pms – CVP) gradient*.

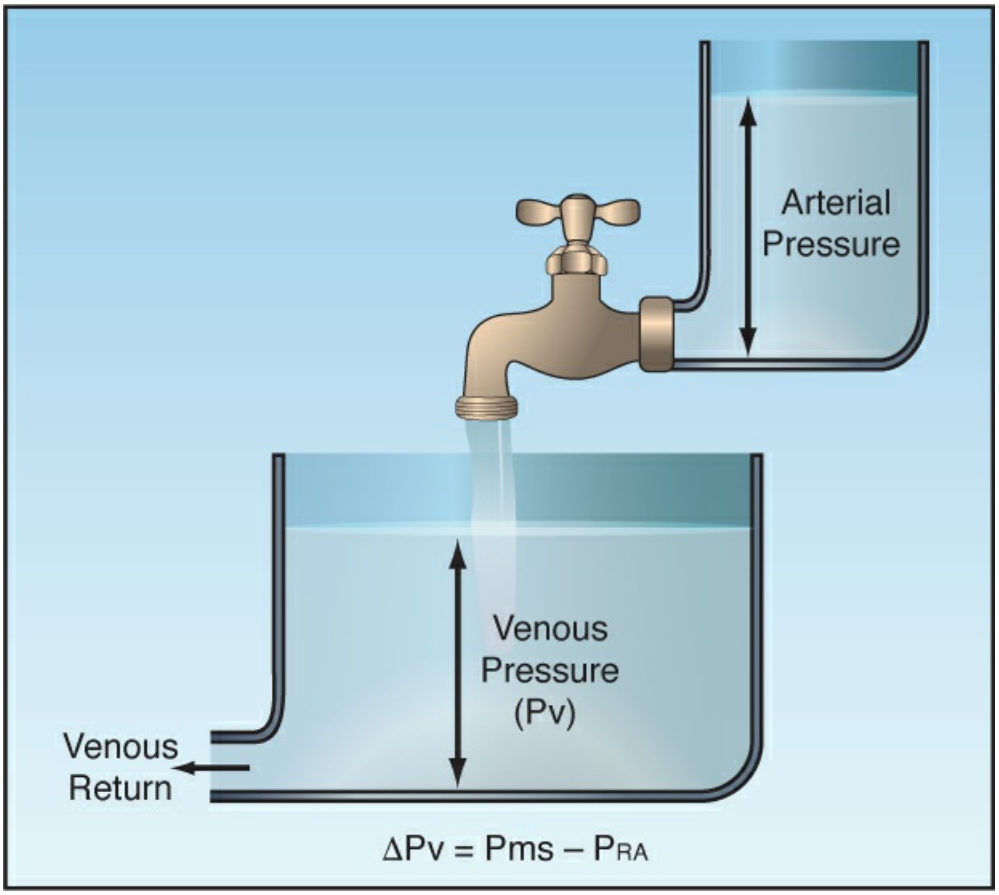

FIGURE 11.1 Illustration to demonstrate how the pressure gradient for venous return (ΔPv) is distinct from the pressure in the arterial circulation. Pms = mean systemic pressure, PRA = right atrial pressure. See text for explanation.

Central Venous Pressure

One of the traditional goals of fluid resuscitation has been an increase in the CVP (7). However, the relationships in Equation 11.2 indicate that *an increase in the CVP (i.e., right atrial pressure) will impede venous return*. This is shown in Figure 11.2. The lines in this graph are constructed by varying the right atrial pressure (PRA) independently (i.e., without a change in blood volume) and recording the resulting changes in blood flow (venous return). Note that progressive increases in PRA above zero are associated with a steady decline in venous return: an increase in PRA of 1 mm Hg results in an average 14% decrease in venous return (8). When venous return eventually ceases, the PRA is equivalent to the Pms, and there is no pressure gradient for venous return. Note that changes in intravascular volume (i.e., hypo- and hypervolemia) are associated with the same directional change in Pms, indicating that Pms is volume-dependent.

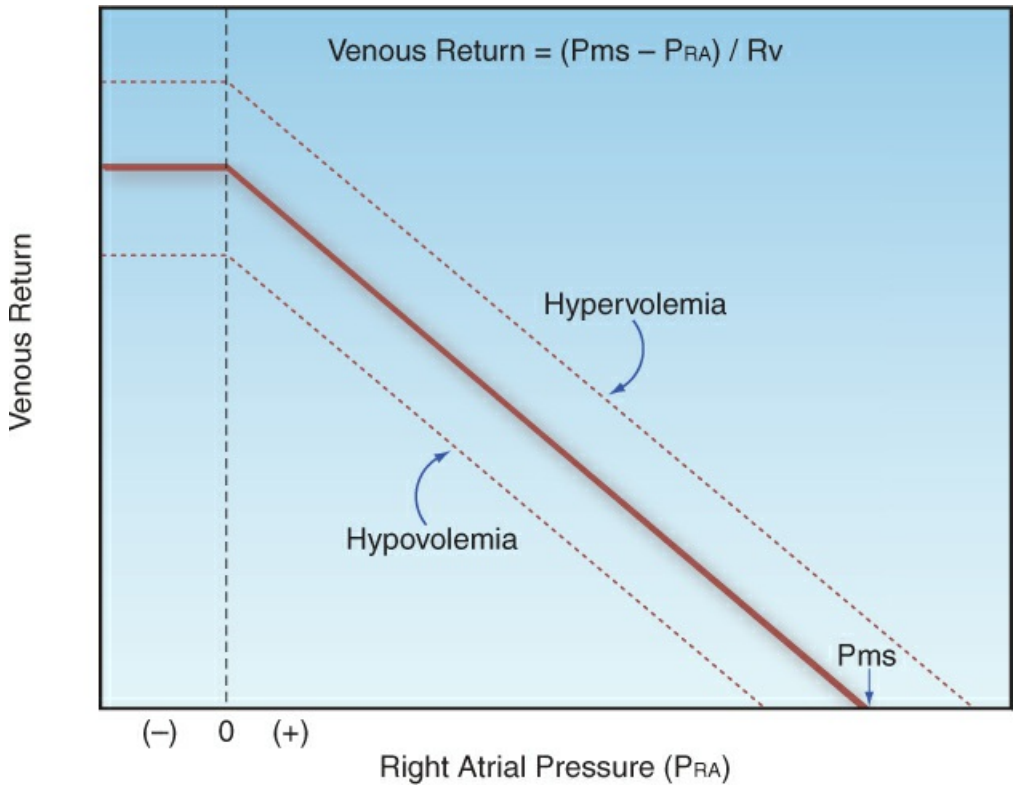

FIGURE 11.2 Graph showing the influence of right atrial pressure on venous return. The normal curve is indicated by the solid line. When venous return is zero, the right atrial pressure (PRA) is equivalent to the mean systemic pressure (Pms). See text for explanation.

Mean Systemic Pressure

The Pms is not easily measured, which may explain why there are relatively few reports of Pms measurements. The original studies involved laboratory animals, and identified a normal Pms of 7–8 mm Hg (8). Human studies have mostly involved postoperative ICU patients (some receiving vasopressors), and have reported Pms values in the 14–20 mm Hg range (9,10). The following is a brief description of two methods used to measure the Pms (9).

Stop-Flow Method

The easiest method of measuring the Pms requires an indwelling radial artery catheter and an inflatable arm cuff with a rapid cuff inflation system (D.E. Hokanson, Inc., Bellevue, WA). The cuff is placed on the upper arm and is inflated (in 0.3 sec) to a pressure that is 50 mm Hg higher than the systolic pressure recorded with the radial artery catheter. This creates a no-flow condition, and after 30 seconds of equilibration time, the radial artery pressure is equivalent to the Pms (9). The cuff is then deflated, and the measurement is repeated for a total of three measurements: the pressures should not vary by more than 5% (9).

Inflation-Hold Method

This method is restricted to ventilator-dependent patients with a regular cardiac rhythm who are also heavily sedated or not breathing spontaneously, and it requires CVP monitoring and a rapid method of measuring the cardiac output (see the section on "Fluid Responsiveness"). The basic principle is to increase the intrathoracic pressure with an "inflation-hold" maneuver (where the inflation volume is held in the lungs at end-inspiration), which will increase the CVP and decrease the cardiac output (a surrogate of venous return). A series of inflation-hold maneuvers is performed at incremental pressures (e.g., 10, 15, 20 cm H_2O) and each inflation-hold is maintained for 12 seconds. The cardiac output and CVP are recorded in the last 3 seconds of the maneuver, and the resulting values (at each pressure) are used to construct a venous return curve (like the ones in Figure 11.2); extrapolation of the curve down to the x-axis then identifies the Pms (9).

Response to Fluids

Clinical studies have consistently shown that the Pms increases in response to a fluid challenge (typically 250–500 mL) (4,5,9,10), but the increase in Pms alone does not identify a beneficial response to fluids (not if there is a similar increase in the CVP) (4). Rather, *patients who are "fluid responsive" are identified by an increase in the (Pms – CVP) gradient after a fluid challenge* (4,10), as predicted by Equation 11.2.

PROBLEMS WITH FLUID RESUSCITATION

This section highlights some of the perceptions and practices that contribute to the problem of iatrogenic fluid overload.

Plasma Volume

The target of fluid resuscitation is the plasma volume, but little consideration is given to the actual plasma volume, or the relatively small deficit that can trigger fluid resuscitation. The size of the plasma and interstitial fluid compartments are shown in Table 11.1, using estimated volumes for an average-sized adult male and female. (For the derivation of these volumes, see Table 10.1.) The total extracellular volume is 16 liters in the male, and 10 liters in the female. Plasma accounts for only 20% of the extracellular fluid, so the plasma volume is only 3 liters in the male, and 2 liters in the female. (*Note:* For a quick estimate of plasma volume, use 40 mL/kg lean body weight in males, and 36 mL/kg in females.)

TABLE 11.1 Representative Fluid Volumes in Average-Sized Adults

Fluid	Male: 75 kg	Female: 60 kg
Extracellular Fluid	16 L	10 L
Interstitial Fluid	13 L	8 L
Plasma	3 L	2 L
Clinically Significant Volume Deficit†	450 mL	300 mL

See Table 10.1 for the derivation of the fluid compartment volumes. Weights represent lean body weight. †A 15% decrease in plasma volume. From References 8 and 9.

Hypovolemia is usually clinically silent until the volume deficit reaches 15% of the blood volume (11), and this is the point that typically triggers fluid resuscitation. As shown in Table 11.1, this corresponds to a plasma volume deficit of 450 mL in the average-sized male, and 300 mL in the average-sized female. Thus, fluid resuscitation can be initiated for volume deficits of only a few hundred milliliters, and failure to consider this can lead to excessive fluid infusion.

Measuring the Plasma Volume

Although rarely used, there is a clinically validated method of measuring blood volume that uses an indicator-dilution technique with iodine-131-labeled albumin to measure plasma volume, and then calculates red cell and blood volumes based on the hematocrit (12). A specialized analyzer (BVA-100®, Daxor Corporation, Oak Ridge, TN) provides results in about one hour, which includes a comparison of the measured and normal or expected volumes. The use of this methodology in patients with septic shock provided the data shown in Figure 11.3 (13). In this case, there was a considerable increase in plasma and blood volume, which corroborates the prevalence of fluid overload in critically ill patients, and provides useful information for guiding fluid management. This approach has also been adopted for the management of acute heart failure, where measurements of plasma volume are used to guide diuretic therapy (14).

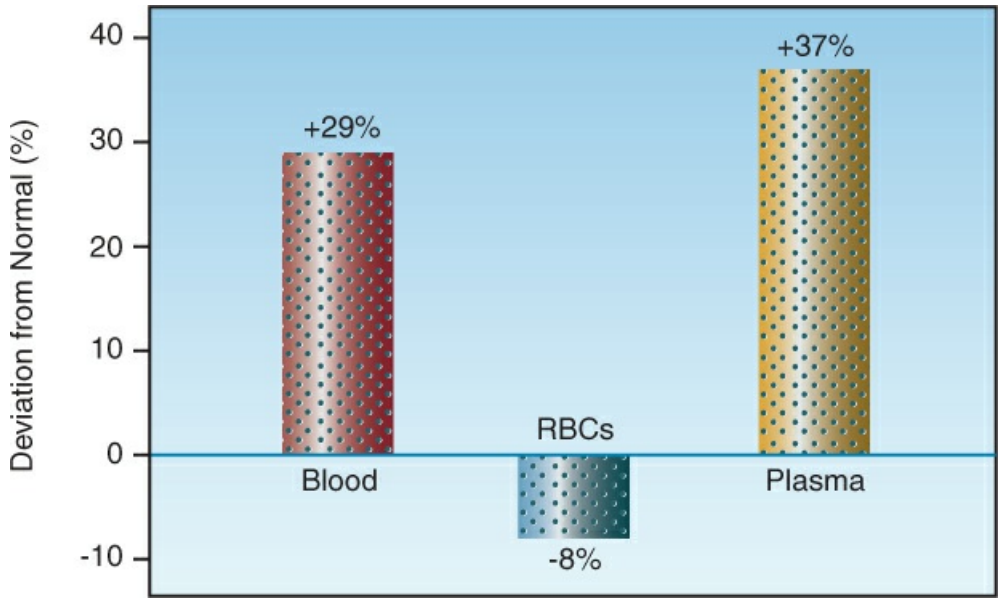

FIGURE 11.3 Measurements of plasma, red cell, and blood volume in 50 patients with septic shock, which provides evidence of iatrogenic fluid overload in critically ill patients. Height of the bars represent mean values. Data from Reference 13.

Distribution of Crystalloid Fluids

The propensity of fluid resuscitation to promote edema formation is largely due to the distribution of infused crystalloid fluids (which is described in detail in Chapter 10). Standard intravenous fluids are electrolyte (predominantly sodium chloride) solutions that distribute uniformly in the extracellular fluid, and since plasma represents 20% of the extracellular fluid (as shown in Table 11.1), then 20% of an infused crystalloid fluid will distribute in plasma, and the remaining 80% will distribute in the interstitial fluid (15). In other words, *the predominant effect of crystalloid fluids is to expand the interstitial fluid volume, not the plasma volume, and this promotes edema formation.*

EXAMPLE: The edema-forming propensity of crystalloid fluids can be demonstrated using the fluid volumes in Table 11.1. The 75 kg adult male has a plasma volume of 3 liters and a volume deficit of 450 mL (15% of the plasma volume). To replace this volume deficit with a crystalloid fluid (e.g., Ringer's lactate) will require 450/0.2 = 2.25 liters, and 1.8 liters of this fluid (2.25 × 0.8) will add to the interstitial fluid volume. Thus, replacing about half a liter of plasma has added almost two liters to the interstitial fluid.

Aggravating Factors

The tendency for crystalloid fluids to promote edema formation will be magnified by two conditions that are common in critically ill patients: i.e., hypoalbuminemia and increased capillary permeability. Albumin is responsible for 80% of the colloid osmotic pressure in plasma (the osmotic force that holds water in the intravascular compartment) (16), and thus hypoalbuminemia will promote the movement of water from plasma to interstitial fluid. Increased capillary permeability is a feature of severe inflammatory conditions, such as septic shock (described in Chapter 17) and the acute respiratory distress syndrome (described in Chapter 24). Both aggravating conditions often coexist, which adds considerably to the negative consequences of crystalloid fluid resuscitation.

Adding Colloid Fluids

Colloid fluids like 5% albumin are much more effective than crystalloid fluids for expanding the plasma volume (see Figure 10.1), and combining colloid and crystalloid fluids has been proposed for reducing the volume of infused fluids (2). This deserves attention.

Assessment of Intravascular Volume

Another major problem in fluid management is the limited ability to accurately assess the intravascular volume. The clinical evaluation of intravascular volume is so flawed that is has been called a "comedy of errors" (17). The following are some of the shortcomings.

Vital Signs

Vital signs are notoriously unreliable for the assessment of intravascular volume, especially in critically ill patients. The following are some relevant observations:

. Tachycardia in the supine position is not observed in most cases of acute blood loss, even when the volume deficit is as high as 25% (18,19). In fact, bradycardia may be more common than tachycardia after acute blood loss (18).

. Supine hypotension does not appear until the blood volume deficit is >30% (11).

. An orthostatic increment in heart rate (≥30 bpm) is the most sensitive marker of hypovolemia, and appears when volume deficits reach 15% (18,19).

These observations indicate that tachycardia and hypotension in the supine position are insensitive markers of hypovolemia. The orthostatic increment in heart rate has limited value in the ICU, because many patients are unable to stand to perform the measurement.

Central Venous Pressure

Central venous pressure (CVP) has traditionally played a dual role in fluid resuscitation, both as a marker of intravascular volume and a target of volume resuscitation. However, neither is justified; i.e.,

. The CVP is not a reliable marker of intravascular volume. This is demonstrated by the scatterplot in Figure 11.4 where each data point represents a paired measurement of the CVP and the circulating blood volume in a group of postoperative patients (20). There is clearly no defined relationship between the two measurements, as confirmed by the correlation coefficient (r) and p value in the upper left corner of the graph. This observation has been confirmed in other studies (21).

. The CVP should not be a target of volume resuscitation, as an increase in the CVP will *impede* venous return. This is explained earlier in the chapter.

The poor correlation between the CVP and blood volume can be attributed to two confounding factors. The first is the influence of right ventricular compliance on the CVP; i.e., a decrease in ventricular compliance (distensibility) will increase the CVP. The second factor is the influence of positive intrathoracic pressure during mechanical ventilation, which is transmitted into the superior vena cava and increases the CVP. This influence can be minimized by measuring the CVP at the end of expiration (see Figure 8.5), but this does not erase the influence of positive end-expiratory pressure (PEEP).

In summary, the information just presented indicates that *the CVP should never be used to make decisions regarding fluid management*.

Inferior Vena Cava Diameter

The evaluation of intravascular volume and fluid responsiveness using respiratory variations in the diameter of the inferior vena cava (as determined by ultrasound) enjoyed a brief period of popularity, but proved to be unreliable (22).

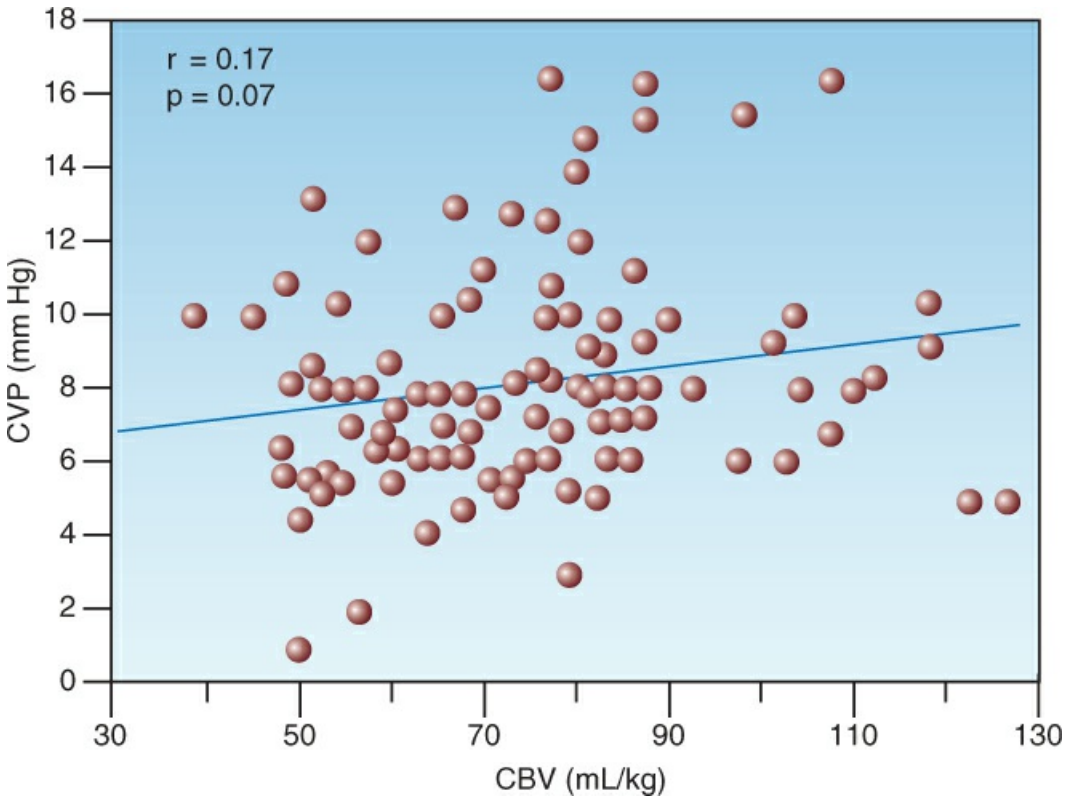

FIGURE 11.4 Scatterplot showing 112 paired measurements of circulating blood volume (CBV) and central venous pressure (CVP) in a group of postoperative patients. Correlation coefficient (R) and p value confirm the lack of correlation between the two measurements. Redrawn from Reference 20.

MARKERS OF TISSUE HYPOPERFUSION

There are two physiological markers of tissue hypoperfusion that can be used to guide fluid resuscitation: the central venous O_2 saturation ($ScvO_2$), and the venoarterial PCO_2 difference (the PCO_2 gap) (23,24). Both measurements require a central venous catheter.

Central Venous O_2 Saturation

(*Note:* This topic is described in Chapter 9, and is only briefly reviewed here.) The venous O_2 saturation (SvO_2) is a reflection of the relationship between O_2 delivery (DO_2) and O_2 consumption (VO_2). This can be explained using the following equation:

$$VO_2 = DO_2 \times (SaO_2 - SvO_2) \qquad (11.3)$$

The term ($SaO_2 - SvO_2$) expresses the extent of hemoglobin desaturation in the systemic microcirculation, also known as "O_2 extraction". The relationships in Equation 11.3 are the basis for the control of VO_2; i.e., when O_2 delivery decreases (e.g., by a decrease in cardiac output), there is a compensatory increase in O_2 extraction, and this helps to maintain a constant VO_2 (and preserve aerobic metabolism). These relationships are demonstrated in Figure 9.3. Note that as

the DO_2 decreases, the VO_2 remains constant until the compensatory increase in ($SaO_2 - SvO_2$) reaches 50% and the SvO_2 drops to 50%. Beyond this point, the VO_2 becomes "supply dependent", which indicates the onset of aerobic metabolism. Note also that when the SaO_2 is constant, the increase in O_2 extraction is equivalent to the decrease in SvO_2.

According to the control system for VO_2 just described, *the SvO_2 will change in the same direction as changes in O_2 delivery*, and thus a decrease in SVO_2 can be used as evidence of a decrease in O_2 delivery. The SvO_2 is ideally measured in "mixed venous" blood in the pulmonary arteries, but the more accessible "central venous" O_2 saturation ($ScvO_2$) in the superior vena cava is the popular measure. The $ScvO_2$ can differ significantly from the mixed venous SvO_2 (see Chapter 9), and trends in the $ScvO_2$ are considered more reliable that individual measurements (25).

Using the $ScvO_2$

The following are some general guidelines for interpreting the $ScvO_2$, which are summarized in Table 11.2 (23). These recommendations are based on the assumption that the VO_2 is constant, and is neither abnormally high or low.

- The $ScvO_2$ is normally about 70–75%, although occasional measurements are as low as 65% or as high as 80% (23).
- An $ScvO_2$ that is <65% is evidence of a decrease in O_2 delivery. However, it is not necessarily evidence of tissue hypoperfusion, because anemia and hypoxemia are other potential causes of a decrease in O_2 delivery. (See Equation 9.8 for the determinants of O_2 delivery.) Hypoxemia is not a common culprit (because it is not allowed to persist), but anemia should be ruled out.
- A decrease in $ScvO_2$ to ≤50% indicates that tissue oxygenation may be threatened or even impaired. In this situation, prompt corrective measures (e.g., fluid resuscitation or red blood cell transfusion) are warranted, and the plasma lactate level should be measured.
- The $ScvO_2$ can be higher than expected in patients with septic shock, and may reach levels above 80%. This is commonly attributed to peripheral shunting from high flow rates, but the most likely source is a defect in O_2 utilization in tissues. (This is described in more detail in Chapter 17.) In this situation, the PCO_2 gap can help to uncover tissue hypoperfusion.

ANEMIA: A decrease in $ScvO_2$ can be a consequence of anemia; an $ScvO_2$ <70% has been proposed as an indication for red blood cell transfusions (26). When the $ScvO_2$ is <65% and anemia is present, the PCO_2 gap can help to determine if hypoperfusion is present.

TABLE 11.2 Markers of Tissue Hypoperfusion

	Normal Range	Tissue Hypoperfusion	Tissue O_2 Threatened
$ScvO_2$	65–75%	<65%	≤50%
PCO_2 Gap	2–5 mm Hg (0.3–0.7 kPa)	>6 mm Hg (>0.8 kPa)	—

The PCO_2 Gap

The PCO_2 gap refers to the difference in PCO_2 between venous and arterial blood, which is a function of blood flow. This can be explained using the Fick principle to derive the rate of CO_2 production (VCO_2); i.e.,

$$VCO_2 = CO \times (CvCO_2 - CaCO_2) \quad (11.4)$$

where CO is cardiac output and ($CvCO_2 - CaCO_2$) is the difference in CO_2 content between venous and arterial blood. The CO_2 content can be expressed as the product of the PCO_2 and a dissociation constant (k), so Equation 11.3 can be rewritten as (23):

$$VCO_2 = CO \times k \times (PvCO_2 - PaCO_2) \quad (11.5)$$

Rearranging the terms then yields the following relationships:

$$(PvCO_2 - PaCO_2) = VCO_2 / CO \times k \quad (11.6)$$

This equation reveals that *the venoarterial PCO_2 difference (the PCO_2 gap), is inversely related to the cardiac output*, and thus a decrease in cardiac output will increase the PCO_2 gap (27).

The PCO_2 gap is thus a reflection of the CO_2 washout from tissues. Carbon dioxide is a major product of metabolism, and must be continually removed in venous blood. Impaired tissue perfusion leads to a buildup of CO_2 in tissues and, because CO_2 is highly diffusible, this results in an increase in the venous PCO_2 (and an increase in the PCO_2 gap).

Using the PCO_2 Gap

The PCO_2 gap is a specific marker of tissue hypoperfusion, and it has been recommended as a target of fluid resuscitation in patients with circulatory shock, including septic shock (23,24,27,28). The following is a summary of the relevant points about the PCO_2 gap.

. The venous PCO_2 in the superior vena cava is used for the PCO_2 gap.

. The normal PCO_2 gap is 2–5 mm Hg (0.3 – 0.7 kPa).

. A PCO_2 gap that is >6 mm Hg (>0.8 kPa) is evidence of tissue hypoperfusion (27).

. The PCO_2 gap provides no information about the adequacy of tissue oxygenation, and a normal PCO_2 gap does not rule out impaired tissue oxygenation.

. The Haldane effect (i.e., hypoxia increases CO_2 binding to hemoglobin) alters the relationship between the PCO_2 and CO_2 content in venous blood, and this can affect the reliability of the PCO_2 gap. However, the clinical significance of this is unclear.

Comment

The PCO_2 gap has two advantages over the $ScvO_2$: 1) It is more specific for detecting tissue hypoperfusion, and 2) the reliability is not affected by septic shock. Because of these advantages,

the PCO_2 gap should be preferred for monitoring tissue perfusion, especially in patients with septic shock or anemia. However, because the PCO_2 gap cannot detect impaired tissue oxygenation, combining both measurements may be the optimal approach in critically ill patients.

FLUID RESPONSIVENESS

Aggressive fluid resuscitation is common in hemodynamically unstable patients, but *only about 50% of hemodynamically unstable patients show a beneficial response to fluids* (i.e., an increase in cardiac stroke output) (29). Therefore, evaluating patients for fluid responsiveness should have a significant impact on iatrogenic fluid overload. It is important to emphasize that *fluid responsiveness does not imply hypovolemia*, since patients who are normovolemic or even hypervolemic can be fluid responsive.

The Fluid Challenge

The standard method for determining fluid responsiveness is to administer a fluid bolus, which is usually *500 mL of a crystalloid fluid infused over 10–15 minutes* (30,31). The rate of infusion is more important than the volume infused (30).

The Response

A positive response to a fluid challenge is defined as a >10% increase in stroke volume (31). This response peaks within minutes after the bolus, and dissipates after 10 minutes (32), which is too evanescent to be measured by the thermodilution technique using pulmonary artery catheters. Two methods of continuous cardiac output monitoring are favored in this situation, as described next.

PULSE CONTOUR ANALYSIS: The arterial pressure waveform can be used to measure the stroke volume, as illustrated in the upper panel of Figure 11.5 (33). The shaded "area under the curve" (AUC) represents the systolic portion of the waveform. The stroke volume is directly related to the AUC, and is inversely related to the cardiac afterload (i.e., aortic compliance and resistance). This method requires an arterial catheter, a suitable arterial pressure waveform, and a regular cardiac rhythm. Measurements obtained with a commercially available monitoring system (FloTrac® System, Edwards Laboratories, Irvine, CA) are accurate in most patients, but can slightly underestimate the stroke volume in conditions of low vascular resistance (e.g., septic shock) (34). However, the system is considered reliable for evaluating fluid responsiveness (34).

ESOPHAGEAL DOPPLER METHOD: Continuous cardiac output monitoring is also possible with a Doppler probe placed in the distal esophagus to measure flow velocity in the descending thoracic aorta. The area under the aortic velocity wave is then multiplied by the aortic cross-sectional area to derive the stroke volume (35). Measurements obtained with this method compare favorably with the thermodilution method of measuring cardiac output (the gold standard) (36), but aortic stenosis produces spurious recordings (35).

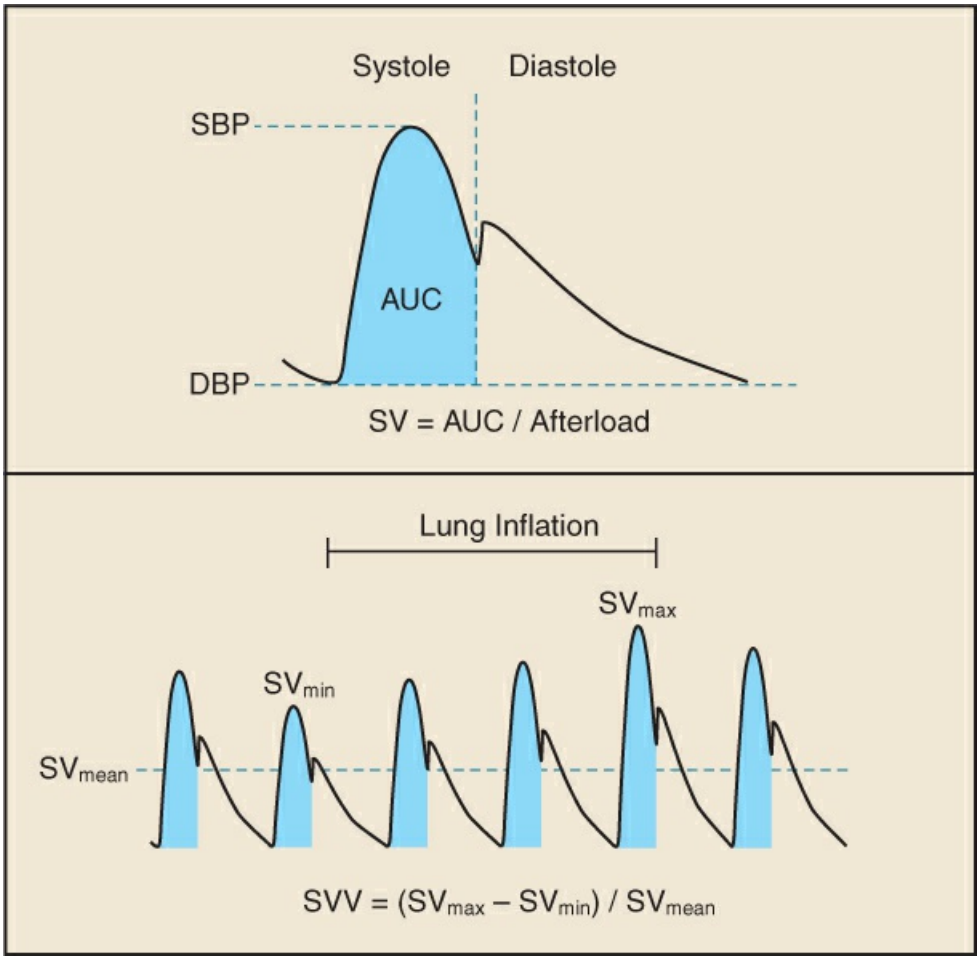

FIGURE 11.5 The upper panel shows the pulse contour method of measuring the stroke volume (SV), where the area under the curve (AUC) represents the systolic portion of the arterial pressure waveform. The lower panel demonstrates the respiratory variation in stroke volume that occurs during mechanical ventilation, and shows how this stroke volume variation (SVV) is quantified. See text for further explanation.

No Fluid Challenge

The use of fluid boluses to evaluate fluid responsiveness can be counterproductive by adding to the problem of fluid overload. This is not a concern with the following "fluid-free" methods of evaluating fluid responsiveness.

Stroke Volume Variation

During controlled mechanical ventilation, the positive-pressure lung inflation is accompanied by an increase in cardiac stroke output, as illustrated in lower panel of Figure 11.5. This is explained by the ability of positive intrathoracic pressure to decrease left ventricular afterload (see Chapter 26), and this effect produces cyclical changes in stroke volume during mechanical ventilation. This stroke volume variation (SVV) can be quantified as shown in Figure 11.5, and clinical studies have shown that an SVV of ≥15% can identify fluid responsiveness in 80% of cases (37). SVV monitoring is restricted to patients who have no breathing efforts and no arrhythmias, and this limits its use.

Passive Leg Raising

Elevating the legs to 45° above the horizontal plane will move about 300 mL of blood out of the lower extremities and towards the heart (38), thereby serving as a “built-in” fluid challenge. This passive leg raising (PLR) maneuver has been shown to promote venous return by increasing mean systemic pressure (39). The subsequent increase in stroke volume is rapid, and can dissipate in minutes (38). A ≥10% increase in stroke volume after PLR has a sensitivity of 85% and a specificity of 92% for identifying a positive response to a fluid bolus (40). False negative results are common in patients with increased intraabdominal pressure (41).

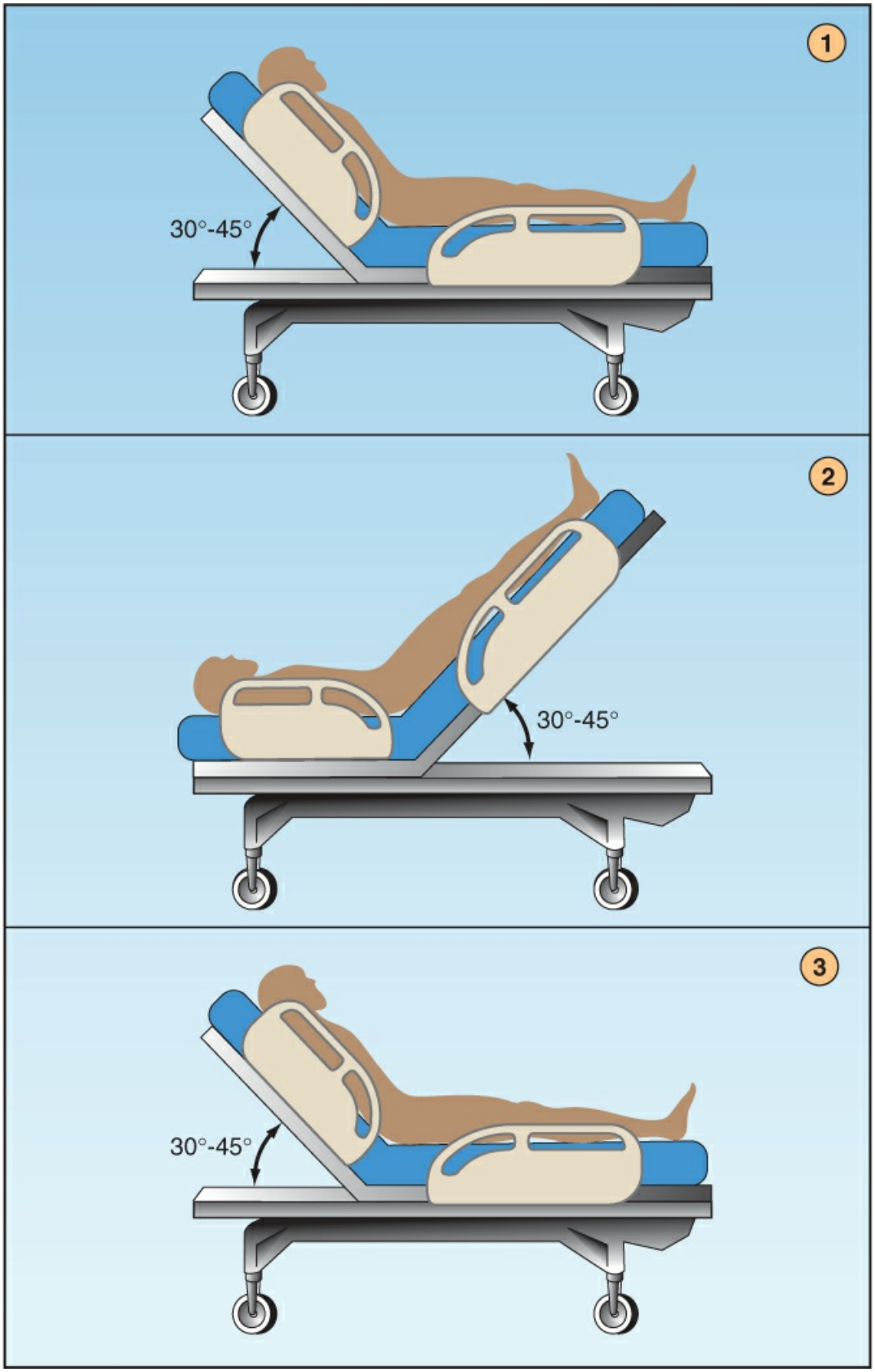

FIGURE 11.6 The passive leg raising test for fluid responsiveness. See text for explanation.

The PLR test is performed on spontaneously breathing patients (on or off the ventilator), and the response is evaluated using a method of continuous cardiac output monitoring (e.g., pulse contour analysis). Blood pressure monitoring alone is not adequate for evaluating the response (38). The test is illustrated in Figure 11.6, and should proceed as follows (using the numbers that correspond to each panel in the figure):

. The patient should be in a semirecumbent position (head up at 30–45°) at the beginning of the test, since starting from the supine position will eliminate the contribution of blood mobilized from the splanchnic circulation (38).
. After baseline measurements of stroke volume, the hospital bed is used to move the patient into a position where the trunk is horizontal and the legs are elevated to 30–45°. (The bed is used for this purpose to reduce pain from shifting positions, which could produce a false positive result.)
. If there is a positive response (i.e., a ≥10% increase in stroke volume) that persists after a few minutes, the patient should be moved back to a semirecumbent position, and the response should dissipate.

As mentioned, pain triggered by the change in position can produce a positive response to PLR, and this should be suspected if the response is accompanied by tachycardia (since PLR should not cause tachycardia) (38), or if the response persists after returning the patient to a semirecumbent position.

Comment

The need for continuous cardiac output monitoring to evaluate fluid responsiveness creates several drawbacks, including costly equipment, the need for trained personnel (for esophageal Doppler monitoring) or a radial artery catheter (for pulse contour analysis), plus a regular cardiac rhythm, and (for monitoring stroke volume variation) patients with little or no spontaneous breathing efforts. Noninvasive methods (e.g., respiratory variations in pulse pressure, changes in end-tidal PCO_2 after passive leg raising) have been evaluated, but none have proven reliable enough to replace existing methods.

Considerations

The goal of determining fluid responsiveness is to reduce the risk of iatrogenic fluid overload, but it seems that this can be achieved with less costly and convoluted methods, such as the ones listed below.

. When aggressive fluid resuscitation is indicated (e.g., for the initial management of hypotension), using a combination of colloid and crystalloid fluids instead of crystalloid fluids alone will reduce the volume requirement.
. If there is no clinical response to the initial period of fluid resuscitation, then prompt de-escalation of the fluid regimen is indicated.
. Avoid daily maintenance fluids if there is adequate oral or enteral fluid intake.
. Pay attention to daily fluid intake and output, and correct positive daily fluid balances

promptly (with a diuretic if needed). This will prevent “fluid creep”, which is a common and often overlooked source of iatrogenic fluid overload (42).

A FINAL WORD

Getting Rid of Fluid

The human body responds to fluid deprivation by conserving salt and water, which is a robust protective response with multiple components (e.g., activation of the renin-angiotensin-aldosterone system, release of ADH). On the other end of the spectrum, our ability to protect against fluid overload seems feeble by comparison. For example, it can take over 2 days to excrete a 2-liter infusion of isotonic saline (43). This discrepancy could be a reflection of fluid control systems that operate at a low baseline level, where activating the system will have a far greater impact than inhibiting it. The sluggish response to fluids could also be a distribution problem, since most of the infused volume of crystalloid fluids is distributed outside the vascular space (where it is unlikely to trigger any type of compensatory response). Whatever the reason, our apparent meager ability to deal with fluid excess emphasizes the value of a conservative approach to intravenous fluid therapy.

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Problems in Fluid Management

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A Final Word

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Section V

BLOOD COMPONENTS

Most ignorance is vincible ignorance:
we don't know because we don't want to know.

Aldous Huxley

Chapter 12

Anemia and Red Blood Cell Transfusions

A conscientious man would be cautious how he dealt in blood.

Edmund Burke (*a*)

As many as 50% of ICU patients are transfused with red blood cells (1), and in a large majority (90%) of cases, these transfusions are used to boost the hemoglobin level in nonbleeding patients (2). The practice of transfusing red blood cells (RBCs) based on the hemoglobin level creates a question about the correlation between the hemoglobin level in blood and the adequacy of tissue oxygenation (since the goal of RBC transfusions should be to promote tissue oxygenation). This is a relevant issue because there are considerable risks associated with RBC transfusions, and there is a concern that these risks may outweigh the risks of the anemia they are meant to correct (3).

This chapter focuses on the influence of anemia and RBC transfusions on tissue oxygenation. It begins by describing the causes and consequences of anemia in the critically ill, and then presents the indications, physiological effects, and adverse consequences associated with RBC transfusions. Current practices that lack a rational or scientific basis are highlighted, to address the need for a more judicious use of RBC transfusions.

ANEMIA IN THE ICU

Anemia is almost universal in the ICU; i.e., it is present on admission in two-thirds of the patients, and the prevalence increases to 97% after one week in the ICU (4). However, the standard definition of anemia can be problematic in ICU patients, as explained next.

Definition of Anemia

Anemia is defined as a *decrease in the oxygen carrying capacity of blood*. The most accurate measure of the O_2 carrying capacity of blood is the *red cell mass*, which is the volume of circulating red blood cells, and is measured using chromium-tagged erythrocytes. This measurement is not typically used in clinical settings; instead, the hematocrit (Hct) and

hemoglobin concentration are used as clinical measures of O_2 carrying capacity. (Reference ranges for these red cell parameters are shown in Table 12.1) *The clinical definition of anemia is a hemoglobin (Hb) concentration <13 g/dL (Hct <40%) in males, and <12 g/dL (Hct <38%) in females* (4). Since this definition is based on a concentration, it will be influenced by the plasma volume.

TABLE 12.1 Reference Ranges for Red Cell Parameters in Adults

Hemoglobin (Hb) Males: 13.5–18 g/dL Females: 12–16 g/dL*	***Mean Cell Volume*** Males: 80–100 x 10^{-15}/L Females: same
Hematocrit (Hct) Males: 40–54% Females: 38–47%	***Red Blood Cell Count*** Males: 4.6–6.2 x 10^{12}/L Females: 4.2–5.4 x 10^{12}/L
Red Cell Mass Males: 26 mL/kg Females: 24 mL/kg	***Reticulocyte Count*** Males: 25–75 x 10^{9}/L Females: same

*Normal range is 1 g/dL lower after the first trimester of pregnancy.

Sources: (1) Walker RH (ed). Technical Manual of the American Association of Blood Banks. 10th ed. Arlington, VA: American Association of Blood Banks, 1990:649–650; (2) Hillman RS, Finch CA. Red cell manual. 6th ed. Philadelphia: FA Davis, 1994;46.

Influence of Plasma Volume

The confounding influence of the plasma volume on a clinical measure of O_2 carrying capacity (Hct) is demonstrated in Figure 12.1. The panel on the left shows the postural changes in Hct in a group of healthy adults (5). Note that there is a 4.1% absolute decrease in Hct in the supine position. This is the result of a decrease in the hydrostatic pressure within the capillaries in the legs (due to loss of the gravitational effect), which promotes the movement of interstitial fluid into the bloodstream and increases the plasma volume (by 420 mL in this study). The panel on the right shows the effect of a bolus infusion of isotonic saline (20 mL/kg), which causes a similar (4.2%) decrease in Hct (6). In both cases, the decrease in Hct is equivalent to the change produced by the loss of one unit of red blood cells.

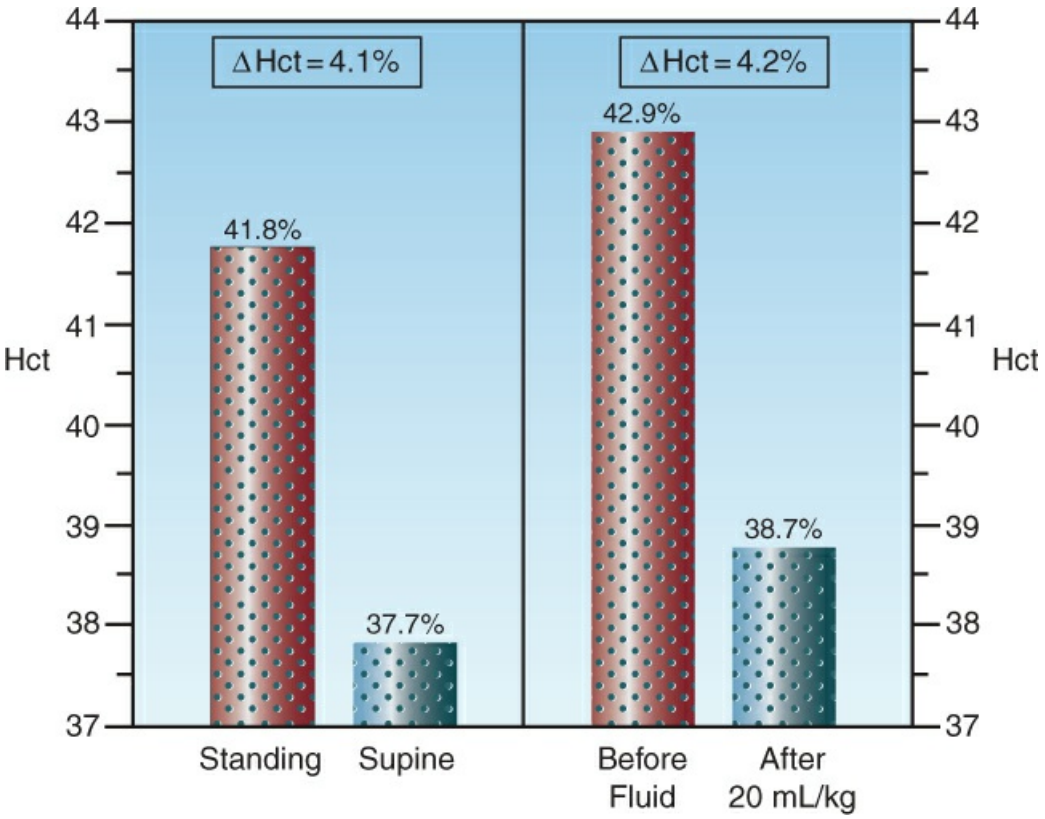

FIGURE 12.1 The influence of plasma volume on the hematocrit (Hct). The panel on the left shows the postural decrease in Hct in the supine position, which is explained in the text. The panel on the right shows the decrease in Hct 90 minutes after a bolus infusion of isotonic saline at 20 mL/kg. In both cases, the absolute decrease in Hct is equivalent to the change produced by loss of one unit of blood (500 mL). From References 6 and 7.

An increased plasma volume is common in critically ill patients, as emphasized in Chapter 11 (see Figure 11.3), and this means that *the Hct and Hb concentration will overestimate the prevalence and severity of anemia in ICU patients*. Clinical studies have confirmed that the Hct and Hb concentration are unreliable measures of anemia in critically ill patients (7,8). Unfortunately, these are the measures used in all the clinical studies evaluating anemia and erythrocyte transfusions in critically ill patients.

ICU-Related Anemia

Two conditions can add to the prevalence and severity of anemia during the ICU stay: systemic inflammation, and repeated phlebotomy for laboratory studies.

Inflammation

Systemic inflammation is accompanied by iron sequestration in tissue macrophages, which is attributed to the actions of cytokines, and also to the hepatic release of *hepcidin* (9), a small peptide that reduces plasma iron levels by promoting iron sequestration in tissue macrophages (9). The sequestered iron cannot be transferred to developing red blood cells, and this results in a hypochromic microcytic anemia that resembles iron-deficiency anemia. (This is the same mechanism for the “anemia of chronic disease”). The plasma iron profile in the *anemia of*

inflammation includes a decrease in plasma iron, total iron binding capacity, and transferrin levels, which can be indistinguishable from iron deficiency, but there is an increase in plasma ferritin levels.

PLASMA FERRITIN: The ferritin level in plasma is used to evaluate tissue iron stores, and thus can distinguish between iron deficiency anemia (plasma ferritin <30 μg/L) and the anemia of inflammation (plasma ferritin >100 μg/L) (9).

Phlebotomy

An average of 40–70 mL of blood is withdrawn daily in ICU patients to perform laboratory tests (4,10), and the cumulative blood loss can reach 500 mL (one unit of whole blood) after one week.

The daily phlebotomy volume can be reduced by reinfusing the initial sample on a blood draw; i.e., when blood is withdrawn through vascular catheters for laboratory testing, the initial aspirate is discarded to eliminate interference from intravenous fluid in the lumen of the catheter. The volume of discarded blood is typically about 5 mL for each laboratory blood draw, and returning this blood to the patient can reduce the daily phlebotomy volume by 50% (11).

The Physiology of Anemia

Anemia elicits two responses that help to preserve tissue oxygenation: (1) an increase in cardiac output (the result of a decrease in blood viscosity), and (2) an increase in O_2 extraction from capillary blood.

Blood Viscosity

Viscosity is defined as the resistance of a fluid to changes in flow rate (12), and has also been described as the "gooiness" of a fluid (13). The viscosity of blood is the result of cross-linking of erythrocytes by plasma fibrinogen, and the principal determinant of whole blood viscosity is the concentration of erythrocytes (the hematocrit). The influence of hematocrit on blood viscosity is shown in Table 12.2. Note that blood viscosity can be expressed in absolute or relative terms (relative to water). The viscosity of plasma (zero hematocrit) is only slightly higher than that of water, while the viscosity of whole blood at a normal hematocrit (45%) is about 3 times greater than plasma and about 4 times greater than water. Thus, anemic blood flows much more readily than normal blood.

TABLE 12.2 Relationship Between Hematocrit and Blood Viscosity

Hematocrit (%)	Relative Viscosity (water = 1)	Absolute Viscosity (centipoise)
0	1.4	—
10	1.8	1.2
20	2.1	1.5
30	2.8	1.8
40	3.7	2.3

50	4.8	2.9
60	5.8	3.8

From Documenta Geigy Scientific Tables. 7th ed. Basel: Documenta Geigy, 1966:557–8.

RESISTANCE TO FLOW: The influence of blood viscosity on peripheral blood flow can be described with the Hagen-Poiseuille equation shown below (14), which is also used in Chapter 1 to describe flow through vascular catheters.

$$Q = \Delta P \times (\pi r^4 / 8\mu L) \quad (12.1)$$

This equation states that flow (Q) through a blood vessel is directly related to the pressure gradient along the vessel (ΔP) and the fourth power of the radius (r) of the vessel, and is inversely related to the length (L) of the vessel and the viscosity (μ) of the fluid. The final term in the equation is the reciprocal of resistance (1/R), so resistance to flow can be described as:

$$R = 8\mu L / \pi r^4 \quad (12.2)$$

This equation indicates that flow resistance in the peripheral circulation is directly related to blood viscosity.

Cardiac Output

The effects of anemia on blood viscosity are responsible for the increase in cardiac output shown in Figure 12.2 (15). Note that the increase in cardiac output is proportionally greater than the decrease in hematocrit. This is because blood is a *non-Newtonian fluid,* which means that viscosity is influenced by blood flow; i.e., an increase in blood flow will reduce viscosity. (In a teleological sense, this property would be advantageous in helping to reduce blood loss through a punctured blood vessel; i.e., blood loss through a puncture would lead to a decrease in local blood flow, which would then "thicken" the blood and reduce the tendency for further blood loss.) The increase in cardiac output helps to maintain systemic O_2 transport in the face of a declining hematocrit.

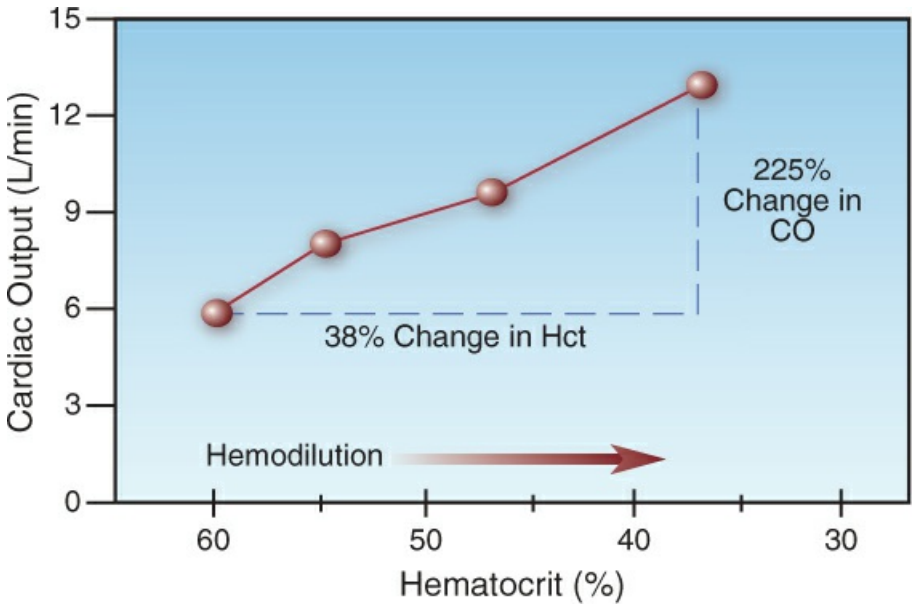

FIGURE 12.2 The influence of progressive isovolemic hemodilution on cardiac output in a patient with polycythemia. From Reference 15.

Systemic Oxygenation

The influence of progressive anemia on measures of systemic oxygenation are shown in Figure 12.3 (16). The principal findings are explained using the following relationships between O_2 uptake (VO_2), O_2 delivery (DO_2), and O_2 extraction:

$$VO_2 = DO_2 \times O_2 \text{ Extraction} \tag{12.3}$$

The upper panel in Figure 12.3 shows that, despite the increase in cardiac output in anemia, the decrease in hemoglobin results in an overall decrease in systemic O_2 delivery. However, there is a compensatory increase in O_2 extraction, and this maintains a constant O_2 uptake (shown in the lower panel). However, when the hematocrit falls below 10%, the increase in O_2 extraction is no longer able to fully compensate for the decrease in O_2 delivery, and the O_2 uptake then begins to fall. When this occurs, the lactate level begins to rise, indicating inadequate tissue oxygenation. Note that the maximum O_2 extraction is about 50 %, and this marks the threshold for impaired tissue oxygenation.

There are two features in Figure 12.3 that deserve emphasis:

. Anemia did not impair tissue oxygenation until the hematocrit fell to 10% (equivalent to a Hb concentration of 3 g/dL), indicating that even the most severe anemias are tolerated (thanks to the compensatory increase in O_2 extraction).

. An O_2 extraction that has increased to 50% marks the point where tissue oxygenation is threatened, and this point could serve as an indication for RBC transfusions. (More on this a little later).

TOLERANCE TO SEVERE ANEMIA: Animal studies have shown that, when the intravascular volume

is maintained, hematocrits as low as 5 to 10% (Hb = 1.5 to 3 g/dL) do not adversely affect tissue oxygenation (16–18), even in awake animals breathing room air (18). Human studies of the lowest tolerable hematocrit or hemoglobin mostly involve Jehovah's Witness (JW) patients. In a large study that included 300 postoperative JW patients, 50% of the patients survived with a Hb level of 2–3 g/dL, and 75% of the patients survived with a Hb level of 3–4 g/dL (19). Another study of progressive hemodilution in healthy adults showed that Hb levels of 5 g/dL produced no apparent harm (20). Thus, the available studies suggest that Hb levels down to 5.0 are safe, and individual patients can tolerate Hb levels as low as 2–3 g/dL!

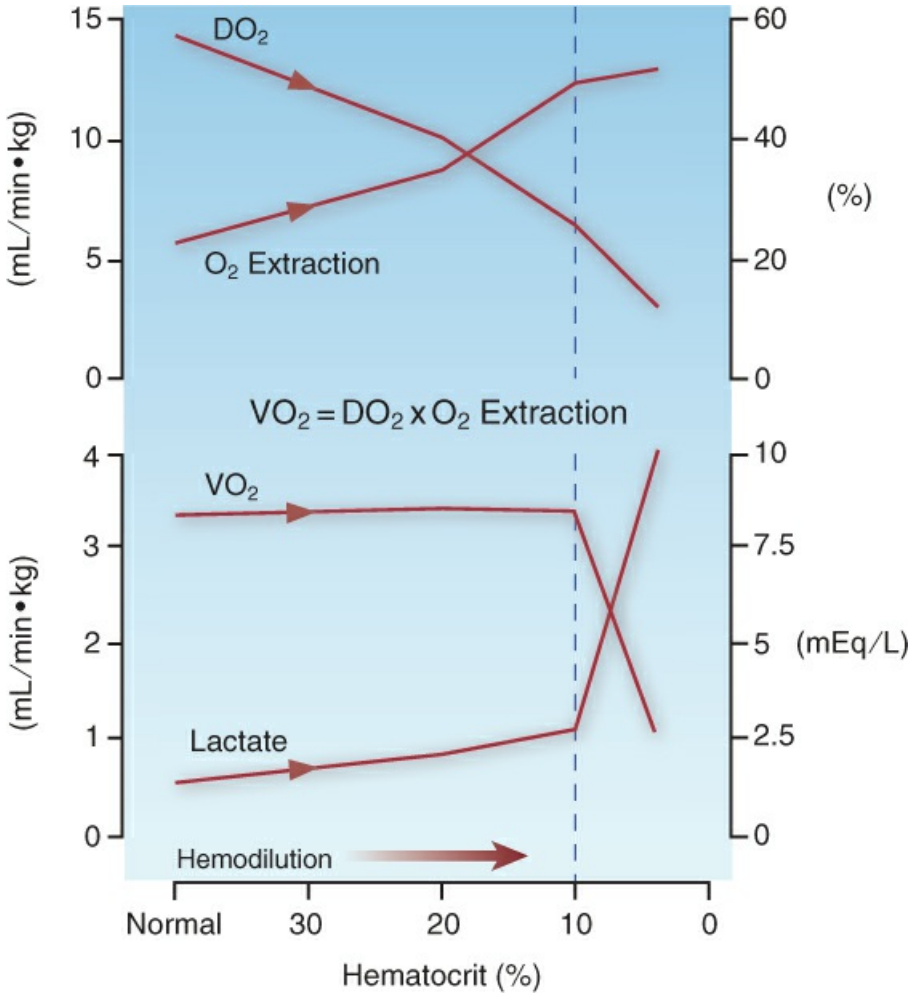

FIGURE 12.3 The influence of progressive isovolemic anemia on measures of systemic oxygenation in nonhuman primates. DO_2 = O_2 delivery, VO_2 = O_2 uptake. See text for explanation. Data from Reference 16.

THE TRANSFUSION TRIGGER

In 1942, a hemoglobin (Hb) level of ≤10 g/dL was recommended as an indication for RBC transfusions (21), and this was the standard *transfusion trigger* for the next 60 years, until concern about the risks associated with RBC transfusions prompted studies which showed that outcomes were not adversely affected if Hb levels were allowed to decrease to 7 g/dL (22,23). A

recent review of 48 clinical studies confirmed that outcomes were similar (including cardiac events) when Hb levels were maintained at 7–8 g/dL instead of 9–10 g/dL, and that the lower Hb threshold for transfusion resulted in a 41% reduction in the consumption of RBC products (24).

Guidelines

There are 21 clinical practice guidelines for RBC transfusions in critically ill patients who are not actively bleeding (for the recommendations of each, see Ref. 25), and the majority of the recommendations state the following:

. The threshold for RBC transfusions is a Hb <7 g/dL for critically ill patients who are hemodynamically stable, and do not have coronary artery disease. This includes post-cardiac surgery patients and patients with septic shock.

. The transfusion threshold should be a Hb <8 g/dL for patients with coronary artery disease, and for patients undergoing cardiac surgery or orthopedic surgery.

Compliance with these guidelines has been poor; e.g., one survey of close to 5,000 RBC transfusions revealed that 60% of transfusions did not follow the recommendations of the guidelines (26).

What's Wrong?

There are two problems with the use of the Hb concentration as a transfusion trigger:

. The Hb concentration provides no information about the adequacy of tissue oxygenation, and since the goal of RBC transfusions is to promote tissue oxygenation, transfusions based on the Hb concentration are given without evidence of need or benefit.

. Acute decreases in the Hb concentration can be a dilutional effect, and this can result in inappropriate RBC transfusions.

Some clinical practice guidelines have recommended abandoning the Hb level as a transfusion trigger and adopting more physiologic measures of tissue oxygenation (27), like the ones described next (27).

Oxygen Extraction

As described earlier (and shown in Figure 12.3) anemia elicits a compensatory increase in O_2 extraction, which helps to maintain a constant rate of O_2 uptake into tissues. However, the O_2 extraction reaches a maximum of about 50%, and beyond this point, further decreases in Hb will result in a decrease in O_2 uptake, which is a marker of impaired tissue oxygenation. Therefore, a*n O_2 extraction of 50% can be used as a transfusion trigger* because it identifies the threshold for impaired tissue oxygenation (28). The O_2 extraction is roughly equivalent to the difference between the arterial and central venous O_2 saturation, (SaO_2–$ScvO_2$), and this can be monitored continuously using pulse oximetry (for the SaO_2) and a central venous "oximetry" catheter (for the $ScvO_2$).

When the SaO_2 is close to 100%, the $ScvO_2$ can be used alone as a transfusion trigger; e.g.,

an $ScvO_2$ <70% has been proposed as a transfusion trigger (29).

Unfortunately, despite the physiological advantages of these approaches, they have received little attention.

RED BLOOD CELL TRANSFUSIONS

Whole blood is stored only on request, and is otherwise separated into its component parts; i.e., red blood cells (RBCs), platelets, plasma, and cryoprecipitate. This practice allows each unit of donated blood to serve multiple transfusion needs.

Preparations

The RBC preparations that are available for transfusion are shown in Table 12.3.

TABLE 12.3 Red Blood Cell Preparations

Preparation	Features
Packed RBCs	1. Each unit has a volume of 350 mL and hematocrit of about 60%. 2. Contains leukocytes and residual plasma (15–30 mL per unit) 3. Can be stored for 42 days with appropriate additives
Leukocyte-reduced RBCs	1. Donor RBCs are passed through specialized filters to remove most of the leukocytes. This reduces the risk of nonhemolytic febrile reactions. 2. Indicated for patients with a history of (nonhemolytic) febrile transfusion reactions
Washed RBCs	1. Packed RBCs are saline washed to remove residual plasma, which reduces the risk of hypersensitivity reactions. 2. Indicated for patients with a history of transfusion-related allergic reactions, and in patients with IgA deficiency, who are at risk for transfusion-related anaphylaxis

From Reference 30.

Packed RBCs

The erythrocyte fraction of donated blood is placed in a preservative fluid and stored at 1 to 6° C. Newer preservative solutions contain adenine, which helps to maintain ATP levels in stored erythrocytes, and allows storage of donor erythrocytes for up to 42 days (30). Each unit of concentrated erythrocytes, known as *packed red blood cells* (packed RBCs), has a hematocrit of about 60% and a volume of about 350 mL, which includes about 30 – 50 mL of residual plasma, and a considerable number of leukocytes (30).

Leukocyte-Reduced RBCs

The leukocytes in packed RBCs can trigger an antibody response in the recipient after repeated transfusions, and this is responsible for febrile nonhemolytic transfusion reactions (see later). To reduce the risk of this reaction, donor RBCs are passed through specialized filters to remove most of the leukocytes. This is performed routinely in many blood banks, but universal leukocyte reduction has yet to be adopted in the United States. Leukocyte-reduced RBCs are recommended for patients with prior febrile nonhemolytic transfusion reactions (30).

Washed RBCs

Donor RBCs can be washed with isotonic saline to remove residual plasma. This reduces the risk of hypersensitivity reactions caused by prior sensitization to plasma proteins in donor blood. Washed RBC preparations are recommended for patients with a history of hypersensitivity reactions to blood transfusions, and for patients with immunoglobulin A deficiency, who have an increased risk of transfusion-related anaphylaxis (30). Saline washing does not effectively remove leukocytes.

Infusing Packed RBCs

Packed RBCs (PRBCs) have a high viscosity (due to the Hct of 60%) and thus have a sluggish flow rate. As a result, saline is often added to PRBC transfusions to increase the flow rate and reduce infusion time. The data in Table 12.4 shows the infusion time for one unit of PRBCs through 18- and 20-gauge peripheral catheters, and the influence of dilution with 100 mL isotonic saline (31). Note that the infusion time is almost 2 hrs when the undiluted RBCs are infused through a 20-gauge catheter, and the infusion time is reduced to almost one hour with an 18-gauge catheter. Also note that the RBCs infuse six times faster when diluted with saline. The recommended infusion time is typically 2 hrs per unit of packed RBCs for hemodynamically stable patients (30), so the saline dilution is probably not necessary when PRBCs are infused to correct anemia.

TABLE 12.4 Gravity-Driven Infusion of Packed red Blood Cells

	Volume	Infusion Time	
		20-G Catheter*	18-G Catheter
1 Unit Undiluted	350 mL	117 min	70 min
1 Unit + 100 mL Isotonic Saline	450 mL	19 min	12 min

* G = gauge size. Catheter length 1.2 inches for all infusions. From Reference 31.

Blood Filters

Standard blood filters (pore size 170 to 260 microns) are required for the transfusion of all blood products (30). These filters trap blood clots and other debris, but they do not trap leukocytes, and are not effective for leukocyte reduction (30). These filters can become an impediment to flow as they collect trapped debris, and sluggish infusion rates are an indication to replace filters.

Effects on Systemic Oxygenation

In an average-sized adult, one unit of packed RBCs is expected to raise the hemoglobin concentration and hematocrit by 1 g/dL and 3%, respectively (30). The effects of RBC transfusions on measures of systemic oxygenation are shown in Figure 12.4 The data in this figure is from a group of postoperative patients with severe normovolemic anemia (Hb <7 g/dL) who were transfused with 1 – 2 units of packed RBCs to raise the Hb above 7 g/dL. The RBC transfusions increased the mean Hb concentration from 6.4 to 8 g/dL (25% increase), and there was a similar increase in O_2 delivery (DO_2). However, the systemic O_2 uptake (VO_2) was

unchanged. The constant VO_2 in the face of an increased DO_2 indicates that O_2 extraction was reduced by the RBC transfusions, as predicted by Equation 12.3. These changes in DO_2 and O_2 extraction are the reverse of the changes produced by anemia, as shown in Figure 12.3.

No Improvement in Tissue Oxygenation

The lack of an effect on VO_2 in Figure 12.4 indicates that *RBC transfusions do not enhance tissue oxygenation*. This has been confirmed in several clinical studies (32–35), and prolonged storage of RBCs can actually *impair* tissue oxygenation after transfusion (36). These studies have prompted the following statement in a clinical practice guideline for red blood cell transfusions (27):

"RBC transfusion should not be considered an absolute method to improve tissue oxygenation in critically ill patients."

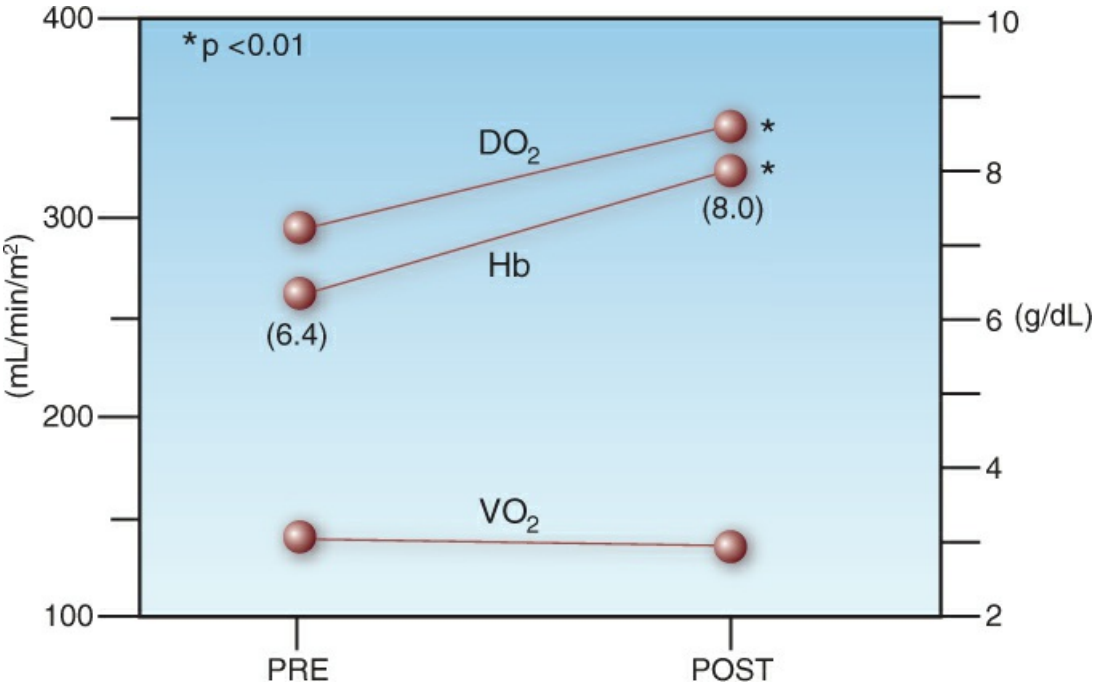

FIGURE 12.4 Effect of RBC transfusions (1–2 units packed RBCs) to correct severe anemia (Hb < 7g/dL) on systemic oxygen delivery (DO_2), and oxygen uptake (VO_2) in 11 postoperative patients. Data points represent mean values for each parameter. Numbers in parentheses indicate the mean hemoglobin concentrations before and after transfusion. Data from personal observations.

COMMENT: The inability of RBC transfusions to enhance tissue oxygenation raises serious questions about the practice of transfusing RBCs simply to boost the Hb level. This concern is especially relevant in light of the multiple risks associated with RBC transfusions, which are described in the next section.

TRANSFUSION RISKS

The spectrum of adverse events associated with RBC transfusions is shown in Table 12.5, along

with the risk of each event per unit of RBCs transfused (37–42). Note that transfusion errors are much more frequent than the feared transmission of infectious agents. The following is a brief description of the principal transfusion reactions.

TABLE 12.5 Adverse Events Associated with RBC Transfusions (per units transfused)

Immune-Related	Others
Nonhemolytic fever (1:60) Hypersensitivity Reactions: Urticaria (1:100) Anaphylaxis (1:1,000) Anaphlyactic shock (1:50,000) Acute lung injury (1:12,000) Nosocomial Infections (?) Acute hemolysis (1:35,000) Fatal hemolysis (1:1.9 million)	Circulatory Overload (1:100)† Transmitted Infections: Bacterial (1:500,000) Hepatitis B virus (1:1.2 million) Hepatitis C virus (1:1.5 million) HIV (1:1.5 million) Transfusion Errors: Wrong person transfused (1:15,000) Incompatible transfusion (1:33,000)

†Estimated risk per recipients rather than units. From References 37–42.

Acute Hemolytic Reactions

Acute hemolytic reactions are prompted by the transfusion of RBCs that are ABO-incompatible with the recipient. When this occurs, antibodies in recipient blood bind to ABO antigens on the donor RBCs, and the ensuing lysis of donor RBCs triggers a systemic inflammatory response that can be accompanied by hypotension and multiorgan failure. *These reactions are usually the result of human error* (43).

Clinical Features

The hallmark of acute hemolytic reactions is the abrupt onset of fever, dyspnea, chest pain, low back pain, and hypotension within minutes after starting the transfusion. Severe reactions are accompanied by a consumptive coagulopathy and progressive multiorgan dysfunction.

Management

. If a hemolytic reaction is suspected, STOP the transfusion immediately and verify that the correct blood was given to the correct patient. It is imperative to stop the transfusion as soon as possible because the severity of hemolytic reactions is a function of the volume of blood transfused (39).

. If the donor blood is correctly matched to the patient, an acute hemolytic reaction is unlikely. However, the blood bank must be notified, and they will ask for blood samples to perform a plasma-free hemoglobin determination (for evidence of intravascular hemolysis) and a direct Coomb's test (for evidence of the anti-ABO antibody).

. If an acute hemolytic reaction is confirmed, the management is general supportive care, with volume support and vasopressors for hypotension, and ventilatory support for respiratory distress. These reactions are rarely fatal (see Table 12.5).

Febrile Nonhemolytic Reactions

Febrile reactions that are unrelated to hemolysis are the most common adverse reactions to RBC transfusions (see Table 12.5). These reactions are characterized by a temperature elevation >1 °C (1.8 °F) that occurs during, or up to 6 hours after, the transfusion, and there is no other apparent cause (e.g., acute hemolytic reaction) (40). The culprit is the presence of antileukocyte antibodies in recipient blood that react with antigens on leukocytes in donor blood. This triggers the release of endogenous pyrogens from phagocytes, which is the source of the fever. This reaction typically occurs in patients who have received prior transfusions, and in multiparous women. Transfusion of leukocyte-reduced RBCs reduces, but does not eliminate, the risk of this reaction (40).

Clinical Features

The fever does not usually appear in the first hour after the start of the transfusion (unlike the fever associated with acute hemolytic reactions), but it can be accompanied by rigors and chills.

Management

. The initial approach to transfusion-related fever is the same as described for hemolytic transfusion reactions, even though the fever may not appear until after the transfusion is completed. The diagnosis is confirmed by excluding the presence of hemolysis with the tests described previously.

. The blood bank will perform a Gram stain on the donor blood, and may request blood cultures from the recipient.

. More than 75% of nonhemolytic fevers will not recur with subsequent transfusions (44). Therefore, no special precautions are needed for future transfusions. If a second febrile reaction occurs, leukocyte-reduced RBCs are advised for all subsequent transfusions.

Hypersensitivity Reactions

Hypersensitivity reactions are the result of sensitization to plasma proteins in donor blood from prior transfusions. Patients with IgA deficiency are prone to hypersensitivity transfusion reactions, and prior exposure to plasma products is not required. The most common hypersensitivity reaction is urticaria, which is reported in one of every 100 units transfused (41). More severe anaphylactic reactions (e.g., bronchospasm) are much less common, and anaphylactic shock is rare

Clinical Features

The usual manifestation is mild urticaria that appears during the transfusion and is not accompanied by fever. The abrupt onset of dyspnea and wheezing during a transfusion could be a sign of an anaphylactic reaction, and hypotension from anaphylactic shock can be mistaken for an acute hemolytic reaction.

Management

. Mild urticaria without fever does not require interruption of the transfusion. However, the

popular practice is to stop the transfusion temporarily and administer an antihistamine for symptom relief (e.g., diphenhydramine, 25–50 mg PO, IM, or IV).

. Severe anaphylactic reactions should be managed as described in Chapter 17. The transfusion should be stopped immediately if severe anaphylaxis is suspected.

. For patients who experience an allergic reaction, washed RBCs should be used for all future transfusions, and for patients who experience an anaphylactic reaction, future transfusions should be avoided unless absolutely necessary.

. Patients who develop hypersensitivity reactions should be tested for an underlying IgA deficiency.

Acute Lung Injury

The condition known as *transfusion-related acute lung injury* (TRALI) is an inflammatory lung injury that resembles the acute respiratory distress syndrome (ARDS), and is associated with RBC and platelet transfusion. It is uncommon (one case per 12,000 RBC transfusions), but is considered the leading cause of transfusion-related deaths, and has a mortality rate that approaches 50% (45).

Etiology

In 80% of cases, TRALI is the result of antibodies in donor blood that bind to antigens on circulating neutrophils in the recipient (45). This triggers neutrophil activation, and the activated neutrophils become sequestered in pulmonary capillaries and migrate into the lungs to produce the inflammatory injury. Antibodies are not involved in about 20% of cases, but the responsible agent has not been identified.

Clinical Features

TRALI presents with acute hypoxemic respiratory failure that often appears in the first hour after the transfusion begins, but can appear anytime in the first 6 hours after the start of the transfusion (46), Fever is common, and the chest x-ray can eventually look like the one in Figure 12.5, with extensive infiltration in both lungs that is indistinguishable from ARDS (which is described in Chapter 24). The respiratory failure can be severe at the outset, and often requires mechanical ventilation.

TRALI can be difficult to distinguish from the hydrostatic pulmonary edema in transfusion-associated circulatory overload (described next), which can appear in the same time frame after the onset of transfusion and can even be accompanied by fever (45). Evidence of systemic inflammation (elevated C-reactive protein) will support the diagnosis of TRALI, along with the absence of heart failure or fluid overload (45).

Management

. If the transfusion is not completed, it should be stopped at the first signs of respiratory difficulty. The blood bank should be notified for all cases of suspected TRALI. (Assays for antileukocyte antibodies are available, but are not routinely used).

. The management of TRALI is supportive, and is similar to the management of ARDS described in Chapter 24.

. There are no firm recommendations regarding future transfusions in patients who develop TRALI. Some recommend using washed RBCs to remove antibodies from donor blood, but the effectiveness of this measure is unknown.

Hydrostatic Pulmonary Edema

The most common pulmonary complication of red blood cell transfusions is a condition known as *transfusion-associated circulatory overload* (TACO), which has a reported incidence of 1% (45,46). The hallmark of this condition is acute hydrostatic pulmonary edema that appears in the first 6 hours after the transfusion begins. The resulting acute hypoxemic respiratory failure often requires mechanical ventilation, and the reported mortality rate is 20% (46).

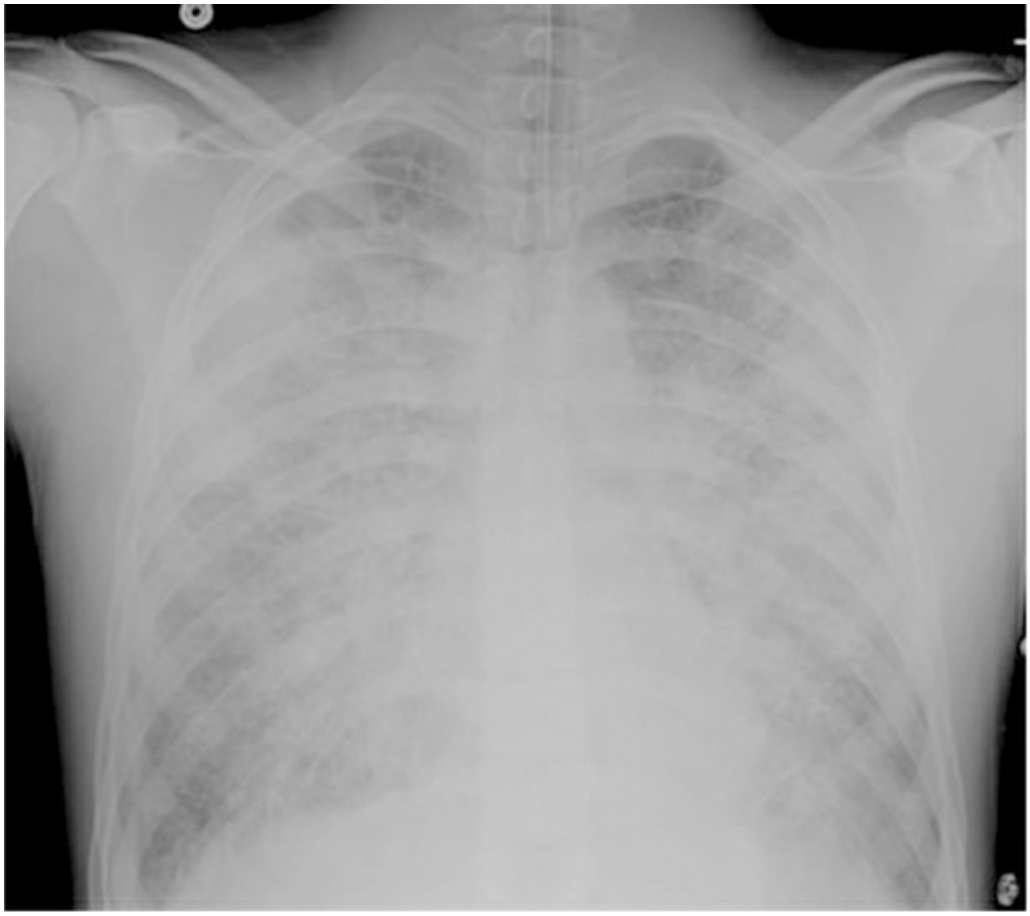

FIGURE 12.5 Portable chest film from a patient with transfusion-related acute lung injury. Note the homogeneous pattern of infiltration in the lungs, which is a characteristics of inflammatory lung injury.

Etiology

There is no correlation between the number of transfused units and the appearance of TACO (46), but the condition appears more frequently in patients with pre-existing heart failure and renal failure, who are prone to fluid overload (45,46). It is also possible that factors other than the infusion volume are operative in this condition.

Clinical Presentation

The clinical presentation can be indistinguishable from TRALI, with acute onset of hypoxemic respiratory failure in the first 6 hours after the transfusion begins, and a chest x-ray that shows pulmonary edema. Patients are febrile in 30% of cases (45), and mechanical ventilation is required in three-quarters of patients (46). Conditions that favor the diagnosis of TACO include pre-existing heart failure, evidence of fluid overload, or underlying renal insufficiency.

Management

. The transfusion should be stopped if not completed, and the blood bank should be notified.

. An intravenous loop diuretic is appropriate. Otherwise, the care is supportive (e.g., with mechanical ventilation, if needed), similar to the management of TRALI.

. There are no recommendations regarding future transfusions, although identifying and correcting a positive fluid balance (with diuretics) prior to transfusions is advised.

Nosocomial Infections

The immunosuppressive effects of blood transfusions became evident with the discovery (in the early 1970s) that pre-transplant blood transfusions improve the survival rate of renal allografts (47). Since then, a multitude of clinical studies have shown that *patients who receive blood transfusions have a higher incidence of nosocomial infection*s (42,48,49). The risk of infection increases with the volume of blood transfused, and with the storage time of donor blood (49). There is a possibility that patients who receive blood transfusions are sicker and thus more prone to infections, but at least 22 studies have shown that blood transfusion is an independent risk factor for nosocomial infections (49).

What's Worse – Anemia or RBC Transfusions?

A review of 45 clinical studies involving RBC transfusions for anemia in critically ill patients, which included 272,596 patients, revealed the following (50):

. In 42 of the 45 studies, the risks of RBC transfusions outweighed the benefits, and only one study showed that the benefit of RBC transfusions exceeded the risks.

. Eighteen studies evaluated the impact of RBC transfusions on survival, and 17 of the 18 studies showed that RBC transfusions were an independent risk factor for a fatal outcome.

Not a very good report card for the use of RBC transfusions to increase the hemoglobin concentration. Wouldn't diuresis do the same thing?

A FINAL WORD

Blood Volume vs. Blood Cells

The practice of boosting hemoglobin levels in critically ill patients is rooted in the belief that anemia is a significant threat to tissue oxygenation. However, it seems that even extreme

reductions in hemoglobin or hematocrit do not impair tissue oxygenation when the intravascular volume is maintained (which allows the cardiac output to increase in response to anemia). Blood volume may have supremacy over the hemoglobin and hematocrit for supporting tissue oxygenation, because hypovolemia is a recognized cause of shock (a state of impaired tissue oxygenation), but anemia is not.

The importance of blood volume is often overlooked in discussions of anemia and RBC transfusions, even by the American Red Cross, whose popular slogan, *blood saves lives*, deserves a more accurate upgrade, as shown in Figure 12.6.

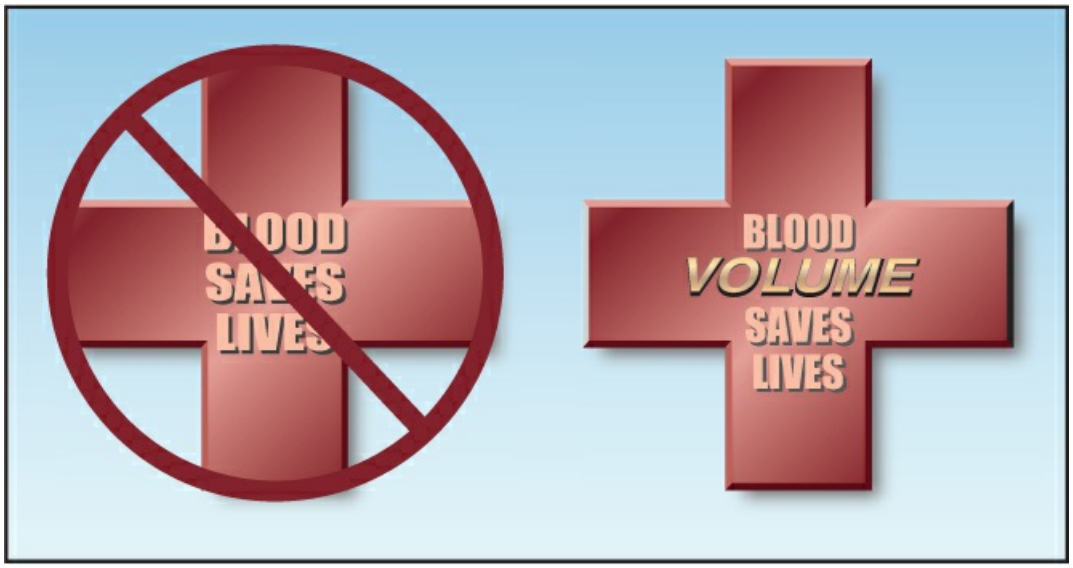

FIGURE 12.6 A popular slogan of the American Red Cross on the left, and an amended version on the right that recognizes the importance of intravascular volume for survival.

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Chapter 13

Platelets and Plasma

Hemorrhage upon a strong pulsation in wounds is bad.

Hippocrates *Aphorisms,* 400 B.C.

The ability to form blood clots is important for limiting blood loss from disrupted blood vessels, which is all the more important if you consider that the human body has a relatively small blood volume (which accounts for only 11–12% of the total body fluids), and loss of as little as 35% of this volume can be fatal (see Chapter 15). Two of the vital components in the complex pathway to clot formation are the circulating platelets and the procoagulant proteins in plasma. This chapter will focus on the dysfunction of these components in critically ill patients, including the causes, consequences, and corrective actions.

OVERVIEW OF HEMOSTASIS

The vascular endothelium is a thromboresistant surface that is covered with a protective meshwork of mucopolysaccharides called the *glycocalyx* that has two principal functions (1,2). First, it limits the passage of large protein molecules from the plasma, thereby maintaining the colloid osmotic pressure of plasma. Second, it maintains the "fluidity" of blood by preventing leukocytes and platelets from adhering to the endothelial surface, and by acting as a mechanoreceptor for sheer stress that signals endothelial cells to secrete nitric oxide, which promotes vasodilation.

Response to Injury

When the endothelium and its protective glycocalyx is disrupted, platelets adhere to exposed collagen in the subendothelium and begin to form a *platelet plug,* which is the primary stage of hemostasis (3). The platelets release calcium, which activates the glycoprotein receptor IIb/IIIa complex on the platelet surface. This receptor complex binds irreversibly to von Willebrand factor on the surrounding endothelial cells, which helps to anchor the platelet plug to the vessel wall. The IIb/IIIa receptor complex also binds fibrinogen, and the subsequent formation of fibrin bridges between adjacent platelets stabilizes the platelet plug, and eventually leads to its contraction, which promotes the resurgence of blood flow.

Fibrin is essential for the stability of a developing thrombus, and there are two pathways to fibrin formation (4). The major pathway is called the *Tissue Factor Pathway* (formerly called the Extrinsic Pathway), and is activated by the release of thromboplastin from the subendothelium. The second pathway is the *Contact Activation Pathway* (formerly called the Intrinsic Pathway), and is activated by endogenous peptides known as kininogens, which are precursors of bradykinin. Both pathways involve the activation of specific procoagulant proteins known as *clotting factors*, and they both lead to the activation of prothrombin (factor II) and the subsequent conversion of fibrinogen (factor I) to fibrin monomers. This is the secondary stage of hemostasis.

The end-product of the response to injury is the *thrombus*, which is essentially a clump of platelets embedded in a meshwork of fibrin strands and anchored to the vessel wall in the area of injury.

THROMBOCYTOPENIA

Thrombocytopenia is the most common hemostatic disorder in critically ill patients, with a reported incidence as high as 60% (5,6). The traditional definition of thrombocytopenia is a platelet count below 150,000/μL, but the ability to form a hemostatic plug is retained until the platelet count falls below 100,000/μL (6), so a platelet count <100,000/μL is more appropriate for identifying clinically significant thrombocytopenia. However, *the risk of major bleeding is not determined by the platelet count alone*, but also requires a structural lesion that is prone to bleeding. In the absence of such a lesion, platelet counts as low as 5,000/μL can be tolerated without evidence of major hemorrhage (7). The major risk with platelet counts <10,000/μL is spontaneous intracerebral hemorrhage, which is uncommon (6).

Pseudothrombocytopenia

Pseudothrombocytopenia is a condition where antibodies to EDTA (the anticoagulant in blood collection tubes) produce clumping of platelets in vitro. The clumped platelets are misread as leukocytes by automated machines that perform cell counts, and this results in a spuriously low platelet count. This phenomenon has been reported in 2% of platelet counts performed in hospitalized patients (8).

Suspicion of pseudothrombocytopenia is usually prompted by a platelet count that is lower than expected, or by the presence of clumped platelets on the peripheral blood smear. If suspected, blood collection tubes that use citrate or heparin as an anticoagulant should be used for subsequent platelet counts.

Critically Ill Patients

The most likely causes of thrombocytopenia in the ICU setting are listed in Table 13.1. The sepsis syndrome is the most common cause of thrombocytopenia in ICU patients, which is the result of increased platelet destruction by macrophages (9). Other less common but more life-threatening causes of thrombocytopenia include heparin and the thrombotic microangiopathies; i.e., disseminated intravascular coagulation (DIC), thrombotic thrombocytopenia purpura (TTP), and the hemolytic-uremic syndrome (HUS).

Drugs like antineoplastic agents can produce thrombocytopenia by suppressing platelet

production, but the most common mechanism for drug-induced thrombocytopenia is the production of antibodies that cross-react with platelets (10). This immune-mediated thrombocytopenia is most frequently observed with heparin, and less frequently with platelet glycoprotein receptor (IIb/IIIa) antagonists, and selected antibiotics (particularly linezolid, β-lactams, and vancomycin).

TABLE 13.1 Causes of Thrombocytopenia in the Critically Ill

Nonpharmacological	Pharmacological
Cardiopulmonary Bypass	Anticonvulsants:
Disseminated intravascular coagulation (DIC)	Phenytoin
Hemolytic-Uremic Syndrome	Valproic acid
HIV Infection	Antimicrobial Agents:
Intra-aortic Balloon Pump	β-Lactams
Liver Disease/Hypersplenism	Linezolid
Malignancy	TMP/SMX
Massive Transfusion	Vancomycin
Renal Replacement Therapy	Antineoplastic Agents
Sepsis Syndrome†	Antithrombotic Agents:
Thrombotic thrombocytopenia purpura (TTP)	Heparin IIb/IIIa Inhibitors
	Histamine H_2 Blockers
	Miscellaneous Drugs:
	Amiodarone
	Furosemide
	Thiazides
	Morphine

†The most common cause of thrombocytopenia in the ICU setting. From References 5,6,9,10.

HEPARIN-INDUCED THROMBOCYTOPENIA

Heparin-induced thrombocytopenia (HIT) is an immune-mediated condition that is associated with life-threatening thrombosis (arterial or venous) in 25% to 70% of cases (11), and has a mortality rate as high as 30% if left unnoticed (12). The incidence of HIT varies from <1% to 5% (11), and is determined by the type of heparin used and the patient population (see later).

Pathogenesis

Heparin is not immunogenic itself, but it binds to a protein (platelet factor 4) on platelets to form an antigenic complex that can trigger the formation of IgG antibodies. These antibodies bind to platelets and induce a strong platelet activation response that promotes thrombosis. The reticuloendothelial system can clear antibody-coated platelets, which helps to limit the incidence of thrombosis. Heparin-associated antibodies usually disappear within 3 months after discontinuing heparin (12).

Risk Factors

The immune response that triggers HIT *is not a dose-dependent reaction*, and can occur with relatively minor heparin exposures from heparin-based catheter flushes or even heparin-coated catheters (11,13). The risk factors associated with HIT include orthopedic or cardiac surgery, obesity, and exposure to unfractionated heparin; i.e., the risk of HIT with unfractionated heparin (UFH) is 2–10 times greater than the risk with low-molecular-weight heparin (LMWH) (11).

HIT is not common in the general ICU population: i.e., the reported incidence of HIT is <1% in critically ill patients, regardless of the type of heparin used (for DVT prophylaxis) (14). In contrast, HIT has been reported in 1–3% of patients in a cardiothoracic ICU when UFH is used (11).

Clinical Features

HIT typically appears 5 to 10 days after the first exposure to heparin, but it can appear within 24 hours in patients who have had a prior exposure to heparin within the past 3 months (11). Although uncommon, a delayed-onset HIT has been reported that becomes evident up to 3 weeks after exposure to heparin (11). Platelet counts in HIT can fall by 50%, but they rarely fall below 20,000/μL.

The feared consequence in HIT is thrombosis, not bleeding. Reports indicate that 17% to 55% of patients with untreated HIT develop venous thromboembolism, and 1% to 3% of patients develop arterial thromboses, which can result in ischemic stroke or acute myocardial infarction (15). *In up to 25% of cases, the thrombosis precedes the thrombocytopenia* (15).

Diagnostic Testing

There are two assays used for the diagnosis of HIT. The first is an enzyme-linked immunosorbent assay (ELISA) for antibodies to the platelet factor 4-heparin complex. This assay has a high sensitivity but a limited specificity, so a negative assay can be used to exclude the diagnosis of HIT, but a positive assay does not confirm the diagnosis (11). The false positive ELISA assays are caused by antibodies to the platelet factor-4 heparin complex that do not activate platelets to produce thrombocytopenia or thrombosis.

The most reliable assay for the diagnosis of HIT is the platelet serotonin-release assay (SRA), which measures the ability of the patient's plasma to activate platelets (which results in enhanced serotonin release by the platelets) (16). This is considered the "gold standard" test for the diagnosis of HIT, and is recommended to confirm the diagnosis of HIT when the ELISA test is positive (16). However, the SRA is not routinely available in many hospitals. As a result, the diagnosis of HIT is usually based on a positive HIT antibody (ELISA) assay.

Risk Assessment

The diagnostic approach to HIT begins by assessing the probability of HIT being present, and a popular risk assessment tool is the 4Ts scoring system shown in Table 13.2 (17). The 4Ts score should be used as follows (18).

. If the probability of HIT is low on the 4Ts score, then nothing further is needed, including laboratory testing for HIT or discontinuing heparin.

. If there is an intermediate-risk on the 4Ts score, then heparin should be discontinued and a non-heparin anticoagulant should be initiated. The ELISA immunoassay for HIT antibodies

should be ordered; if the test is negative, the non-heparin anticoagulant can be discontinued, and heparin can be restarted.

. If there is a high-risk of HIT, then heparin should be discontinued and a non-heparin anticoagulant should be started at full therapeutic doses. This can be discontinued if the ELISA test is negative.

. Patients with a positive ELISA test for HIT antibodies who have no clinical evidence of thrombosis should have an ultrasound evaluation for deep vein thrombosis in the legs. If a central venous catheter is in place, an ultrasound evaluation for thrombosis in the upper extremities is recommended.

. All patients with HIT should receive a non-heparin anticoagulant at full therapeutic doses, even if there is no evidence of associated thrombosis. This recommendation is based on studies showing a 10-fold higher incidence of thrombosis following the appearance of HIT when anticoagulation is delayed (13).

TABLE 13.2 The 4Ts Score for Estimating the Risk of HIT

Conditions	Points
Thrombocytopenia:	
• PLT fall >50% AND nadir ≥20 k/μL AND no surgery past 3 days	2
• PLT fall 30–50% OR nadir = 10–19 k/μL	1
• PLT fall <30% OR nadir <10 k/μL	0
Timing of onset after heparin exposure:	
• Onset at 5–10 days OR ≤1 day if exposure in past 5–30 days	2
• Possible onset at 5–10 days OR >10 days OR, ≤1 day if exposure 31–100 days ago	1
• Onset <4 days without exposure in past 100 days	0
Thrombosis or other adverse reactions:	
• New thrombosis OR skin necrosis OR anaphylactoid reaction	2
• Suspected, progressive, or recurrent thrombosis	1
• None of the above	0
Other causes for thrombocytopenia:	
• None apparent	2
• Possible	1
• Definite	0
Scoring: ≤3 points = Low risk of HIT (<1%) 4–5 points = Intermediate risk (≈10%) 6–8 points = High risk (≈50%)	

Alternative Anticoagulants

Note: Warfarin is absolutely contraindicated in patients with acute HIT because it has a prothrombotic effect that can lead to limb gangrene and necrotic skin lesions (11). Vitamin K reversal is indicated for any patient with HIT who has received warfarin within a few days of the diagnosis.

The alternative anticoagulants for patients with HIT include argatroban, bivalrudin, fondaparinux, and the direct oral anticoagulants (DOACs). Argatroban is currently the only drug approved for use in HIT in the United States, but the ASH guidelines for HIT (18) recommends bivalrudin for percutaneous coronary intervention in patients with HIT. These guidelines also state that fondaparinux and the DOACs (primarily rivaroxaban) are reasonable options in patients who are clinically stable.

Argatroban

Argatroban is a direct thrombin inhibitor that is given by continuous infusion. The recommended dosing regimen is as follows (20):

. Start the infusion at 1–2 μg/kg/min, and titrate dose to achieve an activated PTT of 1.5 to 3 times normal.

. For hepatic insufficiency, start at 0.5 μg/kg/min.

. No dose adjustment is needed for renal dysfunction.

. Full anticoagulation with argatroban should continue until the platelet count rises above 150,000/μL (18).

Long-Term Management

A DOAC can be used for continued anticoagulation after argatroban treatment is completed. Most of the clinical experience with DOACs in HIT have involved rivaroxaban, which has been successful in preventing thrombosis or the extension of thrombosis (18). The duration of treatment is usually 1–3 months. Following an episode of HIT, patients should be advised to wear an emergency identifier for 3 months, and to avoid heparin for life (18).

THROMBOTIC MICROANGIOPATHIES

The thrombotic microangiopathies are life-threatening clinical disorders that share the following features:

. A consumptive thrombocytopenia.

. Microvascular thrombosis with dysfunction of one or more major organs.

. A *microangiopathic hemolytic anemia* that is not immunogenic in origin, but is the result of erythrocyte disruption in the clot-filled microvasculature. The hallmark of this type of hemolytic anemia is the presence of fragmented red blood cells called *schistocytes* on the peripheral blood smear (see Figure 13.1).

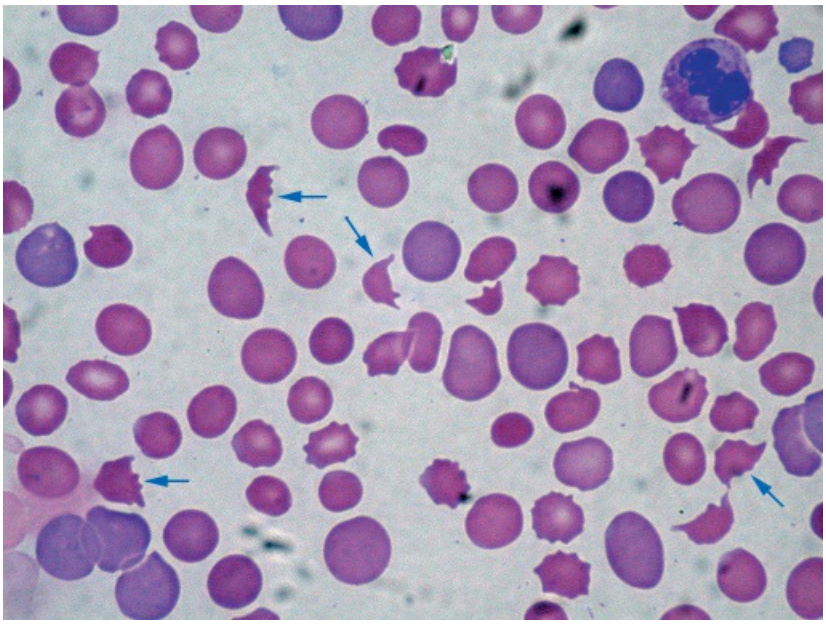

FIGURE 13.1 Peripheral blood smear from a patient with DIC. The arrows are pointing to schistocytes (fragmented erythrocytes) whose presence is pathognomonic of a microangiopathic hemolytic anemia.

There are 3 pathological entities that share these features: disseminated intravascular coagulation (DIC), thrombotic thrombocytopenia purpura (TTP), and the hemolytic-uremic syndrome (HUS). The following is a brief summary of these conditions.

TABLE 13.3 Hematologic Profiles in the Thrombotic Microangiopathies

Feature	DIC	TTP	HUS
Schistocytes	Present	Present	Present
Platelets	Low	Low	Low
INR	Elevated	Normal	Normal
aPTT	Prolonged	Normal	Normal
Fibrinogen	Low	Normal	Normal
Plasma D-dimer	Elevated	Normal	Normal

From Reference 4. DIC = disseminated intravascular coagulation, TTP = thrombotic thrombocytopenia purpura, HUS = hemolytic uremic syndrome.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a secondary disorder that is triggered by conditions that produce widespread endothelial and tissue injury such as multisystem trauma, septic shock, and obstetric emergencies (amniotic fluid embolism, abruptio placentae, eclampsia, and retained fetus syndrome). The inciting event is release of *tissue factor*, which activates a series of clotting factors in the bloodstream that culminates in the formation of fibrin. This leads

to widespread microvascular thrombosis and secondary depletion of platelets and clotting factors, resulting in a *consumptive coagulopathy* (21).

Clinical Features

The microvascular thrombosis in DIC can lead to multiorgan dysfunction, most often involving the lungs, kidneys, and central nervous system, while depletion of platelets and coagulation factors can promote bleeding. Thrombosis is most prominent when sepsis is the underlying cause, while bleeding is prominent in the obstetric conditions. A severe form of DIC known as *purpura fulminans* is characterized by necrosis and gangrene of the limbs, and is seen with overwhelming infections, most notably with meningococcemia (22).

HEMATOLOGIC ABNORMALITIES: The hematologic features of DIC are summarized in Table 13.3. The hemolytic anemia is suspected by an elevated LDH and reduced haptoglobin level, and is confirmed by the presence of schistocytes, like the ones in Figure 13.1. What distinguishes DIC from the other thrombotic microangiopathies is the depletion of clotting factors, which prolongs the INR and the activated partial thromboplastin time (aPTT). Fibrinolysis is also enhanced, which elevates the fibrin degradation products in plasma (i.e., plasma D-dimers).

Management

There is no effective treatment for DIC, and management involves supportive care and treatment of the underlying cause. Life-threatening hemorrhage prompts replacement therapy with blood products, but this usually does not stop the bleeding, and the addition of platelets and coagulation factors can "add fuel" to the microvascular thrombosis. When DIC is accompanied by multiorgan failure, the mortality rate is ≥80% (21).

Thrombotic Thrombocytopenia Purpura

Thrombotic thrombocytopenia purpura (TTP) is a potentially devastating condition that is treatable, but can be fatal in 24–48 hours if left untreated.

Pathogenesis

One of the components of the hemostatic process is the von Willebrand factor (VWF), a large protein from endothelial cells that promotes platelet adhesion. The activity of VWF is normally controlled by a protease enzyme with the name of ADAMTS-13 that cleaves VWF and reduces its prothrombotic activity. The principal problem in TTP is the appearance of antibodies that inactivate the ADAMTS-13 protease (22), resulting in uncontrolled platelet adhesion and widespread microvascular thrombosis. The trigger for these antibodies is not known.

Clinical Features

TTP usually appears in middle age, and is three times more frequent in women. The classic presentation of TTP is a *pentad of manifestations* that include fever, altered mentation, renal insufficiency, thrombocytopenia, and microangiopathic hemolytic anemia. All 5 of these may not be present at the outset; i.e., fever may be absent, and neurologic symptoms may be mild (e.g., headache) or absent. However, this condition can progress rapidly to multiorgan failure and a fatal outcome.

Diagnosis

Prompt diagnosis of TTP is important because delays in treatment can diminish the chances of survival. A marked decrease in ADAMTS-13 activity in plasma is patho-gnomonic of TTP (22), but this test is not readily available in most hospitals. The presence of thrombocytopenia and schistocytes will signal the presence of a thrombotic microangiopathy. TTP can then be distinguished from DIC because *the INR, aPTT, and fibrinogen levels are normal in TTP* (see Table 13.3), and it can be distinguished from the hemolytic uremic syndrome because the renal insufficiency in TTP is often mild (i.e., the creatinine is usually <2 mg/dL) (22).

Treatment

The treatment of choice for TTP is plasma exchange (23), where blood from the patient is diverted to a device that separates and discards the patient's plasma and reinfuses the patient's erythrocytes with plasma from a healthy donor. About 1.5 times the normal plasma volume is exchanged with each treatment, and this is continued daily until the platelet count returns to normal for 2 consecutive days. Acute fulminant TTP is almost always fatal if untreated, but if plasma exchange is started early (within 48 hours of symptom onset), as many as 90% of patients can survive the illness (23,24).

Hemolytic Uremic Syndrome

As the name indicates, the hemolytic uremic syndrome (HUS) is characterized by the combination of a microangiopathic hemolytic anemia and acute renal failure, in addition to a consumptive thrombocytopenia. HUS can be the consequence of a variety of disorders, but infection is probably the most common predisposing condition, especially infections caused by *Escherichia coli* strains that produce the Shiga toxin, and by *Streptococcus pneumoniae* and the influenza virus (25). Other predisposing conditions include pregnancy, autoimmune disorders (e.g., lupus), the antiphospholipid syndrome, malignancy, and drugs (e.g., quinine, cyclosporin, tacrolimus). There is also an inherited condition known as *atypical HUS* that is characterized by unregulated complement activation (26).

Clinical Features

HUS presents with the triad of thrombocytopenia, acute kidney injury and a microangiopathic hemolytic anemia. Extrarenal manifestations are reported in about 20% of cases of atypical HUS (26), and most frequently are neurologic, ranging from agitation to coma.

The diagnosis of HUS requires evidence of a microangiopathic hemolytic anemia (first suspected by elevated LDH and reduced haptoglobin levels, and then confirmed by the presence of schistocytes). HUS differs from DIC in that there is no consumption of clotting factors in HUS, so the INR and aPTT are normal in HUS. Fibrinolysis is also not enhanced, so the products of fibrinolysis (i.e., D-dimer levels) are not increased (see Table 13.3). HUS can be differentiated from TTP by the severity of the renal insufficiency, which is usually greater in HUS (22).

Management

The management of infection-related HUS involves supportive care and treatment of the underlying infection. In cases of atypical HUS due to unregulated complement activation (see earlier), a monoclonal IgG antibody named eculizumab (which binds to the C5 complement

protein and blocks the prothrombotic effects of complement activation) has had success in reversing the condition (27). If this drug is not available, then plasma exchange is the treatment of choice.

Management of the renal failure in HUS involves the usual measures, including renal replacement therapy if needed. Renal transplantation has been used in atypical HUS.

PLATELET TRANSFUSIONS

Indications

Note: The following recommendations for platelet transfusions do not apply to cases of consumptive thrombocytopenia in the thrombotic microangiopathies (where platelet transfusions can aggravate the microvascular thrombosis).

Active Bleeding

In the presence of active bleeding, platelet transfusions are recommended to keep the platelet count above 50,000/μL (28). For intracranial hemorrhage, the platelet count should be kept above 100,000/μL (28).

Prophylactic Transfusions

The most recent guidelines from the American Association of Blood Banks (AABB) includes the following recommendations for prophylactic platelet transfusions (29):

. In the absence of bleeding, platelet transfusions are recommended when the platelet count is ≤10,000/μL.

. For procedures, the following platelet counts are recommended as thresholds for prophylactic platelet transfusions: 1) <50,000/μL for elective non-neuraxial surgery, 2) <50,000/μL for lumbar punctures, and 3) <20,000/μL for insertion of central venous catheters.

One aspect of these recommendations that deserves mention is that none of them have been validated (e.g., platelet counts as low as 5,000/μL do not provoke spontaneous bleeding, as mentioned earlier). Overall, it is reasonable to state that, *in the absence of active bleeding, the major problem with thrombocytopenia is not the platelet count, but the underlying cause of the thrombocytopenia*.

Platelet Preparations

Platelets are provided either as pooled platelets extracted from multiple units of donated whole blood, or by extracting platelets from a single donor using apheresis techniques. Platelets are stored at room temperature, which limits their shelf life to about 5 days.

Pooled Platelet Concentrates

Platelets are separated from fresh whole blood by differential centrifugation, and the resulting platelet concentrates from multiple (4–6) donors are pooled together prior to storage. The pooled platelet concentrate contains about 38×10^{10} platelets in 260 mL plasma, which is equivalent to a

platelet count of about 130 × 10^9/μL. This is six orders of magnitude higher than the normal platelet count in blood (150–400 × 10^3/μL).

Apheresis Platelets

Apheresis platelets are collected from a single donor, and have a platelet count equivalent to the pooled platelet concentrates. The presumed benefit of single-donor platelet transfusions is a lower risk of transmitted infections and a lower incidence of platelet *alloimmunization* (i.e., developing antibodies to donor platelets, which reduces the effect of platelet transfusions). However, neither of these proposed benefits has been validated (30,31) and in a recent national survey that included over 2 million platelet transfusions (31), adverse reactions were much more common with single-donor (apheresed) platelets compared to multiple-donor preparations (see Table 13.4). In addition, there is no difference in the risk of platelet alloimmunization with single-donor and multiple-donor transfusions when the platelet preparations are "leuko-reduced" (32).

Leukoreduction

Leukocytes in donor blood have been implicated in several adverse reactions to transfusion, and leukocyte removal using specialized filters is now a routine practice for erythrocyte transfusions (see last chapter). Platelet concentrates are not free of leukocytes, and leukocyte reduction in platelet preparations reduces the incidence of febrile reactions, as well as cytomegalovirus transmission (which is transmitted in leukocytes) and platelet alloimmunization (28,32). Because of these advantages, leukocyte reduction is becoming a routine practice for platelet transfusions.

Response to Transfused Platelets

In an average-sized adult with no ongoing blood loss, *the infusion of one unit of platelets (either multiple-donor or apheresed platelets) should raise the circulating platelet count by 35,000 to 50,000/μL at one hour post-transfusion* (26). The increment is about 40% lower after 24 hours, as shown in Figure 13.2 (33).

The increment in platelet count declines with multiple transfusions. This is also shown in Figure 13.2, where the platelet increment is about 25% lower after 5 platelet transfusions (33). This phenomenon of "platelet refractoriness" is the result of antiplatelet antibodies in the recipient directed at ABO antigens on donor platelets. This effect is mitigated by transfusing ABO-matched platelets.

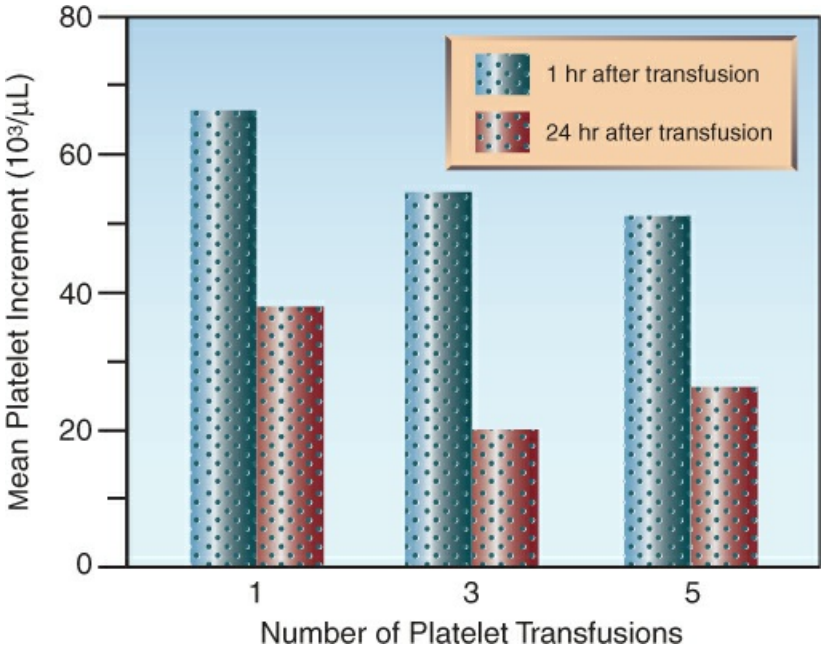

FIGURE 13.2 Post-transfusion increment in platelet counts in relation to the time elapsed after the transfusion (one hour versus 24 hours) and the number of transfusions given. Data from Reference 33.

Adverse Effects

The rate of adverse reactions to platelet transfusions is shown in Table 13.4. The data in this table is from a survey of more than 2 million platelet transfusions, and compares the reaction rates with single-donor and multiple-donor preparations (31). Note the low overall reaction rate, and the higher rate with single-donor preparations. The following are some relevant points about these reactions.

Nonhemolytic Fever

Transfusion-associated fever can be the result of antileukocyte antibodies in recipient blood that react with antigens on leukocytes in donor blood. This triggers the release of endogenous pyrogens from phagocytes, which is the source of the fever. The routine use of leukocyte reduction in platelet preparations has significantly reduced (but not eliminated) this reaction.

Allergic Reactions

Allergic reactions (urticaria, anaphylaxis) are the result of sensitization to plasma proteins in donor blood. Single-donor platelets have a higher plasma volume than multiple-donor preparations, which would explain the higher rate of allergic reactions with single-donor platelets in Table 13.4.

Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is described in Chapter 12. This condition is the result of antileukocyte antibodies in donor plasma that bind to antigens on circulating neutrophils in the recipient. The result is a diffuse, inflammatory lung injury that is similar to the acute respiratory distress syndrome (ARDS). This reaction is most often associated with erythrocyte

transfusions, but also occurs with platelet transfusions.

Transmission of Infections

The adoption of nucleic acid testing has virtually eliminated the risk of transmission of HIV and the hepatitis viruses in both erythrocyte and platelet transfusions. The risk of bacterial transmission is higher with platelet than erythrocyte transfusions because platelets are stored at room temperature, which is more likely to promote bacterial proliferation. However, the rate of bacterial transmission with platelet transfusions is quite low, as shown in Table 13.4.

TABLE 13.4 Adverse reactions to Different Platelet Preparations (Rate per 100,000 Units Transfused)

Adverse Reaction	Multiple-Donor Preparations	Single-Donor Preparations	p value
Nonhemolytic Fever	37	136	<0.01
Allergic Reaction	27	325	<0.01
Acute Lung Injury	1	22	<0.05
Circulatory Overload	7	8	NS
Acute Hemolysis	0.2	1.8	<0.01
Bacterial Transmission	0.8	1.4	NS
Viral Transmission	0	0	NS
Total Reactions	70	478	<0.01

From Reference 31. NS = not significant.

PLASMA PRODUCTS

Plasma products are used as a source of procoagulant plasma proteins, and the two plasma products used most often for this purpose are fresh frozen plasma and cryoprecipitate.

Fresh Frozen Plasma

Plasma is separated from donor blood and frozen at –18° C within 8 hours of blood collection. This *fresh frozen plasma* (FFP) has a volume of about 230 mL, and can be stored for one year. Once thawed, FFP can be stored at 1–6° C (34–43° F) for up to 5 days. The principal uses of FFP include the resuscitation of massive blood loss, and the reversal of anticoagulation with warfarin.

Massive Blood Loss

The current practice for the resuscitation of massive blood loss (i.e., loss equivalent to the blood volume within 24 hours) is to transfuse one unit of FFP for every 1–2 units of packed red blood cells (34). There are two drawbacks with FFP: i.e., the time to thaw FFP is a drawback when immediate availability is needed for the resuscitation effort, and the limited shelf-life after thawing can lead to wasting the product. These limitations have led to the introduction of “liquid

plasma" preparations that are never frozen, and can be stored 1–6° C (34–43° F) for up to 26 days. Early studies of liquid plasma have shown equivalent efficacy with FFP, while also reducing the waste associated with FFP (35).

Prophylactic FFP

A majority of FFP infusions in ICU patients are used to reduce an elevated INR in coagulopathic, nonbleeding patients who are considered at risk for bleeding (e.g., cirrhotic patients with a prior history of variceal bleeding) (36). However, *there is no evidence that prophylactic FFP reduces bleeding* in these patients, or that it provides any type of clinical benefit (37,38).

Reversing Warfarin Anticoagulation

One of the traditional uses of FFP is to replenish clotting factors in cases of troublesome bleeding related to anticoagulation therapy with warfarin. Vitamin K is given first to block ongoing anticoagulant activity, and the FFP is then given (usually in a volume of 10−15 mL/kg) to return the INR to normal (39). This approach has two shortcomings: i.e., the time needed to thaw the FFP leads to treatment delays (which can prolong the bleeding), and the volume of FFP that is required can aggravate the bleeding. These problems have been eliminated by the introduction of *4-factor prothrombin complex concentrate*, a lyophilized powder that contains the vitamin K-dependent clotting factors (factors II, VII, IX, and X) and, with a reconstituted volume of 100 mL, is capable of reversing warfarin effects in less than 30 minutes (40). (See Chapter 47 for more on warfarin reversal.)

FFP and the INR

There is a fundamental problem with the use of the INR to guide FFP infusions. (*Note:* INR is the abbreviation for "international normalized ratio", which is the ratio of the patient's prothrombin time divided by a standardized normal prothrombin time.) This test was introduced to monitor anticoagulation with coumadin, and it is heavily influenced by the activity of the vitamin K-dependent clotting factors (Factors II, VII, IX, and X). However, the INR does not monitor other components of hemostasis, such as the activity of endogenous "anticoagulant" proteins (i.e., antithrombin, protein C, and protein S), which must be considered to determine the overall state of hemostasis.

The graphs in Figure 13.3 show how the INR can be misleading as a guide for FFP infusions (38). The data in these graphs is from a study of prophylactic FFP infusions (12 mL/kg) for an elevated INR in nonbleeding ICU patients who were scheduled for a procedure. Note that the FFP infusions significantly reduced the INR (graph on the left), but they also significantly increased the activity of antithrombin (graph on the right), an anticoagulant protein. (Although not shown, the activity of the other anticoagulant proteins was increased after the FFP infusion.) Thus, despite the favorable effect on the INR, there may be little or no improvement in overall coagulation status because of the opposing effect on endogenous anticoagulant activity.

Adverse Reactions

The adverse reactions to plasma transfusion are similar (in type, not frequency) to the reactions that complicate erythrocyte and platelet transfusions.

Acute Hemolytic Reactions

Acute hemolytic reactions are caused by anti-A and anti-B antibodies in donor plasma that react with A and B antigens on recipient RBCs. Cross-matching of plasma transfusions for ABO compatibility has become a standard practice, which eliminates the risk of acute hemolytic transfusion reactions.

Nonhemolytic Fever

Fever that is unrelated to acute hemolysis is caused by leukocytes in donor blood, which theoretically should not be a risk with plasma transfusions. However, FFP is not free of leukocytes, and this creates a minimal risk of nonhemolytic fever; i.e., in one report, the risk was <1 per 100,000 transfusions (41).

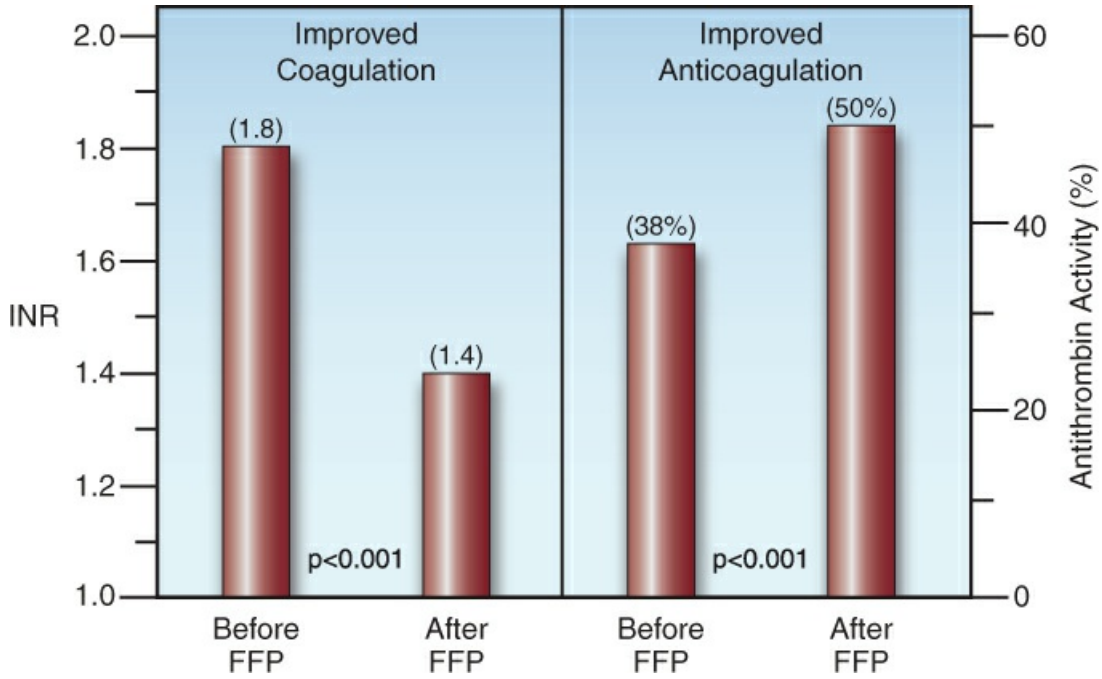

FIGURE 13.3 The influence of FFP (12 mL/kg) on the INR (graph on the left) and the activity of antithrombin (graph on the right) in nonbleeding ICU patients. Height of the bars indicate median values. Despite the favorable decrease in INR, the opposing effect on antithrombin could result in little or no change in coagulation status. Data from Reference 38.

Hypersensitivity Reactions

Hypersensitivity reactions (urticaria, anaphylaxis, anaphylactic shock), which are caused by sensitization to proteins in donor plasma, are more common with plasma transfusions than with erythrocyte or platelet transfusions. The reported incidence of allergic reactions to FFP ranges from 1:600 to 1:2,000 transfusions (41).

Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is attributed to antileukocyte antibodies in donor blood, and is a complication of erythrocyte, platelet, and plasma transfusions. The reported incidence of TRALI with plasma transfusions is about 1:250,000 units transfused (41). The clinical features of TRALI are described in Chapter 12.

Hydrostatic Pulmonary Edema

Transfusion-associated circulatory overload (TACO) is considered a risk if the infusion rate of FFP exceeds 1 mL/kg per hour in patients who are predisposed to circulatory overload (e.g., those with heart failure or pre-existing fluid overload). The reported risk of TACO ranges from 1:70 to 1:1500 units transfused (42).

Transmitted Infections

Plasma transfusions carry a minimal risk of transmitting infections. The risk of hepatitis B transmission is 1:280,000 transfusions, the risk of hepatitis C transmission is 1:1.2 million transfusions, and the risk of HIV transmission is 1:1.6 million transfusions (41). The risk of bacterial transmission is reported as "rare" and CMV transmission, which occurs in transfused leukocytes, has not been reported with plasma transfusions (41).

Cryoprecipitate

When FFP is allowed to thaw at 4° C, a milky precipitate forms that is rich in cold-insoluble proteins (cryoglobulins) like fibrinogen, von Willebrand factor, and factor VIII. This *cryoprecipitate* can be separated from plasma and stored at –18° C for up to one year. It has a fibrinogen concentration of 10–20 g/L, and a storage volume of 10–15 mL. Once thawed, cryoprecipitate must be used within 4 hours (43).

Using Cryoprecipitate

Cryoprecipitate can be used as a source of fibrinogen in massive blood loss from trauma or post-partum hemorrhage. Fibrinogen depletion is always a consideration in the setting of significant blood loss because it is the earliest clotting factor to become depleted, and is also susceptible to the dilutional effects of fluid resuscitation. For major blood loss in trauma, cryoprecipitate is recommended when the fibrinogen level falls to 150–200 mg/dL (44). One unit of cryoprecipitate per 10 kg body weight will increase the plasma fibrinogen level by about 50 mg/dL (43), but this is in the absence of bleeding, so expect a greater cryoprecipitate requirement during active hemorrhage. Alternately, cryoprecipitate administration can be guided by viscoelastic assays, such as thromboelastography (which is described in Chapter 15).

Cryoprecipitate has some drawbacks, including a variable fibrinogen concentration, the time needed for thawing (which can delay infusion and prolong bleeding), and an increased risk of transmitted infections (because it is not subjected to pathogen-reduction measures) (45). These limitations are not shared by *fibrinogen concentrates*, which have a consistent fibrinogen content of 20 g/L, and do not require thawing; as a result, fibrinogen concentrates are gaining popularity as a superior alternative to cryoprecipitate (45).

A FINAL WORD

Changing Perceptions

There are two general messages in this chapter that might change your perception of thrombocytopenia in critically ill patients:

. In the absence of active bleeding, the problem with thrombocytopenia is not the platelet count, but the underlying illness. As a result, prophylactic platelet transfusions are rarely necessary in critically ill patients.

. The most life-threatening consequence of thrombocytopenia is not bleeding, but thrombosis (as is evident in HIT, DIC, TTP and HUS).

And there is one general message that might change your perception of the INR as a measure of coagulation status:

. The INR is sensitive to the activity of vitamin K-dependent coagulation factors, but it does not monitor other components of the hemostatic process, such as the activity of endogenous anticoagulant proteins (i.e., antithrombin, Protein C and Protein S). This limitation affects the reliability of the INR as a gauge for FFP infusions; i.e., a decrease in the INR in response to FFP is considered evidence of an improvement in the ability to form a clot, but FFP also increases the activity of endogenous anticoagulant proteins, and the net result may be little or no change in clot-forming ability. Therefore, the INR provides misleading information for FFP infusions.

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Section VI

SHOCK SYNDROMES

In the successful resuscitation of the shocked patient,
the physician achieves his or her greatest victory.

Evan Geller,
1993

Chapter 14

Approaches to Clinical Shock

Shock is the rude unhinging of the machinery of life.

Samuel Gross, MD (*a*)

One of the recognizable features of the clinical condition known as ”shock” is its name, which lacks any scientific or pathological merit, and is shared by nonclinical entities as far-removed as military operations (”shock and awe”). The clinical use of this term can be traced back to 1731, when a French surgeon named Henri LeDran published his experience with gunshot wounds, and used the term “chock” to describe the injuries that often had fatal outcomes (1). In a subsequent English translation of LeDran’s account, “shock” was mistranslated as indicating the clinical course of the injuries rather than the injuries themselves. Thereafter, ”clinical” shock became synonymous with a life-threatening and rapidly deteriorating condition. However, shock is a consequence of multiple pathological entities, and finding a common ground can be challenging.

This chapter is the first in a series of chapters devoted to clinical shock, and attempts to present a unified view of shock, including what it is, how it is classified, how it presents, and how it is managed. This is followed by three chapters devoted to the major shock syndromes: i.e., hypovolemic, cardiogenic, and septic shock. Simply stated, these conditions are the most challenging you will encounter in the ICU.

WHAT IS CLINICAL SHOCK?

The definition of clinical shock has had many iterations, including the colorful description in the introductory quote by Samuel Gross, one of the titans of surgery in the 19th century who included this description of shock in his popular textbook (*a*). An updated and improved definition of shock would state that *shock is a life-threatening circulatory disorder that is characterized by inadequate cellular oxygen utilization* (2). Shock can be the result of inadequate tissue oxygenation, or inadequate processing of oxygen by mitochondria, but the result is the same; i.e., there is a deficiency in oxidative ATP production. The clinical consequence of this derangement is dysfunction in one or more vital organs, which can progress to multiorgan failure and a fatal outcome.

Clinical Features

The clinical manifestations of shock typically include the following:

. A decrease in blood pressure, which typically results in *hypotension*, defined as a systolic pressure <90 mm Hg or a mean pressure <70 mm Hg (2). (See the next section for more on hypotension in clinical shock.)

. An increase in the plasma lactate level (>2 mmol/L), which is considered evidence of impaired cellular O_2 utilization (although other explanations are available, as described in Chapter 9.)

. Clinical signs of organ dysfunction, which usually begins as *oliguria* (urine output <0.5 mL/kg per hour) and *altered mentation* (e.g., agitation, confusion, or depressed consciousness), and can progress to involve any and all major organs.

. In cases of "low-flow shock", the skin may be cool to touch, and there may be cyanotic changes in the distal extremities. Progression of the low-flow state can produce patchy cyanosis known as "mottled skin" or *livedo reticularis*.

Hypotension

Hypotension has been one of the standard clinical criteria for the diagnosis of clinical shock, but the reliability of hypotension as a marker of clinical shock is questionable, For example, clinical studies have shown that the blood pressure can be normal when there is evidence of inadequate tissue oxygenation (using lactate levels or the central venous O_2 saturation) (3). Furthermore (as anyone who has spent some time in an ICU can verify), hypotension is not always accompanied by evidence of inadequate O_2 utilization in tissues. As a result of observations like these, some consensus guidelines have recommended that hypotension should be abandoned as a marker of clinical shock (4).

Types of Shock

There are 4 different types of shock (shock syndromes), and these can be identified using the following hydraulic relationships: i.e., steady flow (Q) through a closed hydraulic circuit is directly related to the pressure gradient across the circuit (Pin – Pout), and is inversely related to the resistance to flow (R) through the circuit.

$$Q = (Pin - Pout)/R \qquad (14.1)$$

If the hydraulic circuit is the circulatory system, then flow is the cardiac output (CO), the inflow pressure is the mean arterial pressure (MAP), the outflow pressure is the right atrial pressure (RAP), and the resistance to flow is the systemic vascular resistance (SVR). Equation 14.1 is now expressed as follows:

$$CO = (MAP - RAP)/SVR \qquad (14.2)$$

Since a decrease in blood pressure is commonplace in shock, the terms in the above equation can be rearranged to identify the determinants of mean arterial pressure (which is the driving pressure for blood flow):

$$MAP = (CO \times SVR) + RAP \quad (14.3)$$

The different shock syndromes are then identified by the determinants of MAP: i.e.,

a. Low RAP = hypovolemic shock
b. Low CO = cardiogenic shock, obstructive shock
c. Low SVR = vasodilatory shock

The pattern of hemodynamic changes in each type of shock is shown in Table 14.1, along with the reported prevalence of each (2). Note that 3 of the 4 shock syndromes are associated with a low cardiac output and a high SVR. The increase in SVR (i.e., vasoconstriction) is a compensatory response to the low-flow state, and limits the drop in blood pressure. This response is due to increased activity in the sympathetic nervous system, and activation of the renin-angiotensin-aldosterone system.

TABLE 14.1 Hemodynamic Patterns in the Shock Syndromes

Shock Syndromes†	CVP	Cardiac Output	SVR
Hypovolemic (16%)	Low	Low	High
Obstructive (2%)	High	Low	High
Cardiogenic (16%)	High	Low	High
Vasodilatory (66%)	Low	Normal or High	Low

†Numbers in parentheses indicate relative frequency of occurrence (from Reference 2). CVP = central venous pressure, SVR = systemic vascular resistance.

Hypovolemic Shock

Hypovolemic shock is almost always the result of blood loss, and it usually appears when the decrease in blood volume exceeds 30% (5). Dehydration (e.g., from vomiting or diarrhea) does not typically result in shock because the fluid loss leads to an increase in the colloid osmotic pressure of plasma, which draws interstitial fluid into the vascular compartment. Decreases in blood pressure from dehydration are easily corrected with intravenous fluids.

Cardiogenic Shock

Shock from cardiac pump failure is most often the result of acute coronary syndromes, which account for almost half of the cases of cardiogenic shock (6). Less frequent causes include non-ischemic cardiomyopathies (28% of cases) and valvular dysfunction or arrhythmias (17% of cases). Cardiogenic shock presents the greatest challenge in shock management; i.e., despite advances in revascularization and mechanical cardiac support, the mortality rate remains at about 50% (7).

Obstructive Shock

Obstructive shock is caused by conditions that impede or block cardiac filling, such as massive pulmonary embolism, tension pneumothorax, and cardiac tamponade. This condition is

uncommon, and accounts for only 2% of cases of clinical shock (2). Treatment is directed at the responsible condition.

Vasodilatory Shock

Vasodilatory shock (also known as "distributive shock") is a condition of widespread vasodilation involving both arteries and veins. It is the most frequently encountered type of shock (see Table 14.1), and septic shock accounts for most cases. *Septic shock is the leading cause of in-hospital deaths in the United States (8), and is also considered the leading cause of death worldwide* (9). Less common sources of vasodilatory shock include anaphylactic shock, spinal shock, and adrenal crisis.

BLOOD PRESSURE MONITORING

Blood pressure monitoring is mandatory in clinical shock, and direct intra-arterial recordings are preferred.

Direct Recordings

Direct arterial pressure recordings are obtained from the radial, brachial, axillary, or femoral arteries, and the site of cannulation can influence the recorded waveform (see next) .

Arterial Pressure Waveform

The arterial pressure waveform changes as it moves away from the proximal aorta, as shown in Figure 14.1. Note that as the pressure wave moves toward the periphery, the systolic pressure gradually increases and the systolic portion of the waveform narrows. The systolic pressure can increase as much as 20 mm Hg from the proximal aorta to the radial or femoral arteries (10). This increase in peak systolic pressure is offset by the narrowing of the systolic pressure wave, so the mean arterial pressure remains unchanged.

Systolic Amplification

The increase in systolic pressure in peripheral arteries is the result of pressure waves that are reflected back from vascular bifurcations and narrowed blood vessels (11). Reflected waves move faster when the arteries are stiff, and they reach the arterial pressure waveform before it has time to decrement. The convergence of antegrade and retrograde pressure waves then serves to heighten the peak of the pressure waveform. (You can see this effect when ocean waves meet from opposing direction. This magnification effect is implicated in the formation of "monster waves".) Because systolic amplification is the result of retrograde pressure waves, it increases left ventricular afterload, but does not promote systemic blood flow.

Mean Arterial Pressure

The mean arterial pressure (MAP) is the preferred pressure for hemodynamic monitoring for two reasons: it is the principal driving force for systemic blood flow (10,12), and it does not change as the pressure waveform moves peripherally (unlike the systolic pressure). The MAP is measured electronically as the area under the arterial pressure wave, divided by the duration of the cardiac cycle. *The management of clinical shock typically uses a target MAP of ≥65 mm Hg*

(2).

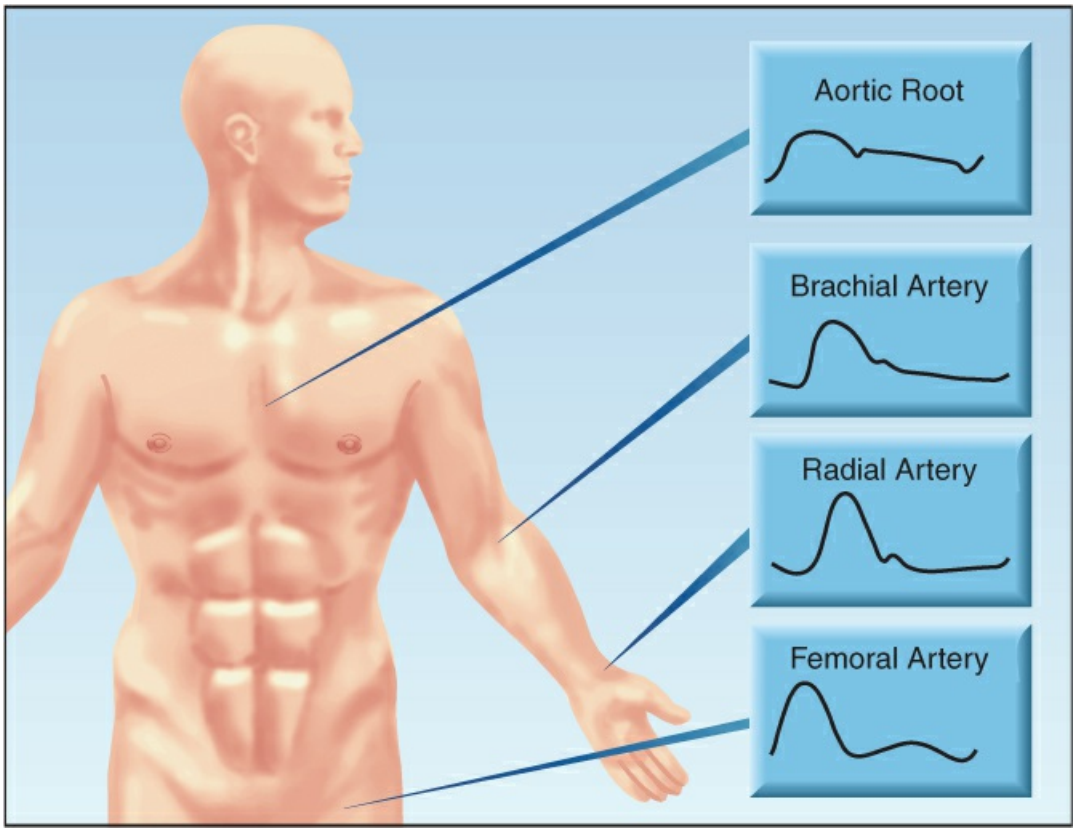

FIGURE 14.1 Arterial pressure waveforms at specific points in the arterial circulation.

Indirect Measurements

Direct blood pressure recordings are not always available, or feasible, and a brief description of indirect pressure measurements is therefore warranted.

The Principle

The indirect blood pressure (BP) measurement uses an inflatable bladder (attached to the underside of a cloth sleeve) that is wrapped around the upper arm or thigh in an area that overlies a major artery. The bladder in the sleeve is then inflated to compress the underlying artery. The effects of arterial compression are illustrated in Figure 14.2. As the cuff pressure increases and the underlying artery is compressed, the pulsations in the artery gradually increase and then decrease until the artery is occluded. These "counterpulsations" produce oscillations in the bladder pressure, and the automated blood pressure devices (which are standard in ICUs) then measure these oscillations and convert them into measures of systolic, diastolic, and mean pressures. This is the *oscillometric method* of measuring the BP. The counterpulsations can also be converted into sound waves, which is the basis for the older *auscultation method* of measuring the BP.

Common Source of Error

Counterpulsations are more reproducible, and BP measurements are more reliable, when an

artery is compressed uniformly. Uniform compression is more likely if the size of the bladder is appropriate for the circumference of the upper arm. The optimal relationships between the height and width of the cuff bladder and the upper arm circumference are shown in Figure 14.3. The following are some important points about the relationship between bladder size and arm size:

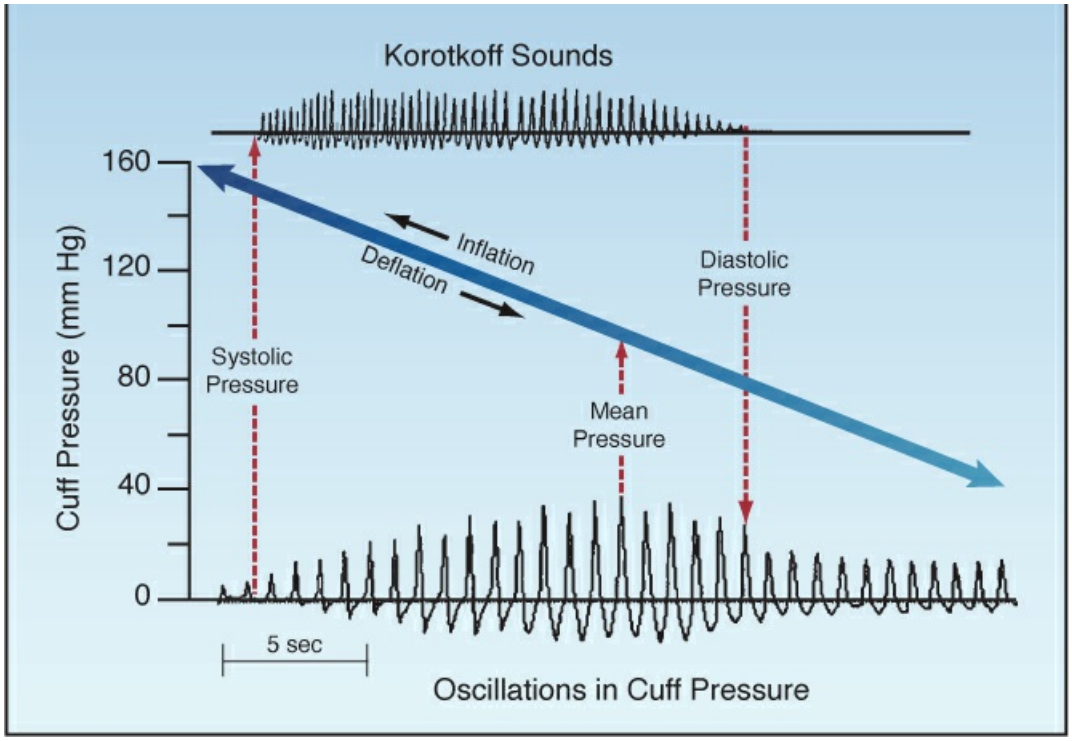

FIGURE 14.2 The oscillometric and auscultatory methods of measuring the blood pressure. See text for explanation.

. To produce uniform arterial occlusion, the length of the inflatable bladder should be at least 80% of the circumference of the upper arm (measured midway between the shoulder and elbow), and the width of the bladder should be at least 40% of the upper arm circumference (13).

. If the inflatable bladder is too small for the size of the upper arm, the pressure measurements will be falsely elevated (1). (Errors in measurement are much less pronounced when the bladder is too large relative to arm circumference.)

. *The use of inappropriately-sized arm cuffs (and their inflatable bladders) is the most common source of error in indirect BP measurements* (13,14). In one study involving ICU patients, two-thirds of the indirect BP measurements were obtained with a cuff size that was inappropriate, and in these cases, 62% of the BP measurements differed from the direct, intra-arterial measurements by more than 10 mm Hg (14).

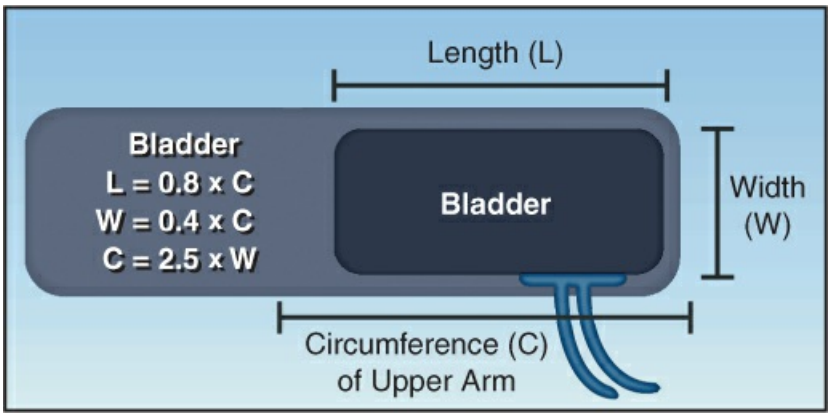

FIGURE 14.3 Optimal relationships between the height (H) and width (W) of the cuff bladder and the circumference (C) of the upper arm.

To help in selecting the appropriate cuff size, Table 14.2 shows the recommended cuff sizes for different sizes of the upper arm (or thigh). An easier way to determine the appropriate cuff size is described next.

TABLE 14.2 Appropriate Size of Blood Pressure Cuff in Relation to Upper Arm Circumference

Upper Arm Circumference	Blood Pressure Cuff	
	Size	Dimensions
22 to 26 cm	Small Adult	12 x 24 cm
27 to 34 cm	Adult	16 x 30 cm
35 to 44 cm	Large Adult	16 x 36 cm
45 to 52 cm	Adult Thigh	16 x 42 cm

From Reference 13.

Simple Method for Assessing Cuff Size

Align the cuff so that the long axis runs along the long axis of the arm. Then turn the cuff over so the bladder on the underside of the cuff is facing upward, and wrap the cuff around the upper arm. The bladder (width) should encircle close to half (40%) of the upper arm. If the bladder encircles less than half of the upper arm, the cuff is too small, and a larger cuff should be used. No change in cuff size is needed if the bladder is too big (i.e., if it encircles most of the upper arm), because this discrepancy does not produce significant errors in measurement (13).

Accuracy

The limited accuracy of indirect BP measurements in critically ill patients is well documented (14,15). This is demonstrated in a recent meta-analysis of 7 studies comparing automated and direct BP measurements in ICU patients (15), which showed that the automated BP measurement could differ from the direct BP by as much as 55 mm Hg (from –15 mm Hg to +40 mm Hg) in individual patients. This is an unacceptable range of variation, and it demonstrates the need for

direct BP recordings in the critically ill.

TISSUE PERFUSION AND OXYGENATION

The approach to shock requires more than blood pressure monitoring, as measures of tissue perfusion and oxygenation are essential for both the detection and management of shock. These measures are shown in Table 14.3, along with the threshold value of each that indicates possible or probable shock. Each of these measures has been described elsewhere in the book, and the following represents only a brief summary.

Oxygen Transport Parameters

There are three measures of systemic oxygen transport: oxygen delivery (DO_2), oxygen uptake (VO_2), and oxygen extraction (VO_2/DO_2). These measures, which are described in detail in Chapter 9, provide an assessment of the global balance between O_2 supply and O_2 demand, which is deranged in all forms of shock.

Cardiac Index

Oxygen transport is dependent on the cardiac output, which is most accurately measured by the thermodilution technique using pulmonary artery catheters (see Chapter 8). Alternative methods include the stroke volume determination from arterial pressure waveforms (see Figure 11.5) or measurements of aortic flow velocity using Doppler ultrasound. (These are described in Chapter 11.) The stroke volume is multiplied by the heart rate to obtain the cardiac output.

As explained in Chapter 8, hemodynamic measurements are typically expressed in relation to body size using the body surface area in meters squared. The size-adjusted cardiac output is called the *cardiac index* (CI), and the normal range is 2.4–4 L/min/m^2 (see Table 8.1). A subnormal CI (<2.5 L/min/m^2) is considered evidence of inadequate tissue perfusion.

Oxygen Delivery

The rate of oxygen delivery in arterial blood (DO_2) is derived as the product of the cardiac index (CI) and the oxygen concentration in arterial blood (CaO_2); i.e.,

$$DO_2 = CI \times CaO_2 \qquad (14.4)$$

(For a more detailed expression of this equation, see Equation 9.8.) *A decrease in O_2 delivery is the culprit in three of the four types of clinical shock (i.e., hypovolemic, cardiogenic, and obstructive shock).* The DO_2 is normally 520–600 mL/min/m^2 (see Table 9.2), and a DO_2 of 300 mL/min/m^2 has been identified as the threshold for inadequate tissue oxygenation (16). However this is not a consistent finding, and some studies have not been able to identify a DO_2 that impairs aerobic metabolism (17).

Oxygen Uptake

The rate of oxygen uptake into tissues (VO_2), which is equivalent to the O_2 consumption, is calculated as the product of the cardiac index and the difference in O_2 concentration between

arterial and venous blood ($CaO_2 - CvO_2$); i.e.,

$$VO_2 = CO \times (CaO_2 - CvO_2) \quad (14.5)$$

(For a more detailed expression of this equation, see Equation 9.10.) The VO_2 is normally 110–160 mL/min/m^2, and an abnormally low VO_2 (<110 mL/min/m^2) is evidence of impaired O_2 utilization (in the absence of aerobic hypometabolism, which is uncommon in critically ill patients).

Oxygen Extraction

Oxygen extraction is the ratio of O_2 uptake to O_2 delivery, which identifies the fraction of delivered oxygen that is taken up into the tissues.

$$O_2 \text{ Extraction} = VO_2/DO_2 \quad (14.6)$$

When the arterial O_2 saturation is close to 100%, Equation 14.6 can be reduced to variables that are easily monitored; i.e.,

$$O_2 \text{ Extraction} = (SaO_2 - ScvO_2) \quad (14.7)$$

where SaO_2 and $ScvO_2$ are the arterial and central venous O_2 saturations, respectively. (For the derivation of this equation, see Equations 9.12–9.14.) This expresses the O_2 extraction as the extent of hemoglobin desaturation as blood flows through the capillaries.

The O_2 extraction is normally 0.2–0.3 (20–30%), and it can increase to about 0.5 (50%) in response to a decrease in DO_2, which helps to keep the VO_2 constant (see Figure 9.3). Further decreases in DO_2 beyond this point will not elicit the compensatory increase in O_2 extraction, and the VO_2 will begin to fall (indicating the onset of anaerobic metabolism). Therefore, an O_2 extraction of ≥50% indicates that O_2 delivery is low enough to threaten, or impair, aerobic metabolism (18). There are also conditions that impair O_2 extraction (e.g., sepsis, liver failure), and these conditions can be identified by an O_2 extraction that is fixed (i.e., does not increase in response to a decrease in DO_2), or is ≤20%. In this situation, the O_2 extraction is not a reliable indicator of changes in O_2 delivery.

Central Venous O_2 Saturation

When the SaO_2 is constant, or is close to 1.0 (100%), Equation 14.7 can be rewritten as:

$$O_2 \text{ Extraction} = (1 - ScvO_2) \quad (14.8)$$

Thus, the central venous O_2 saturation ($ScvO_2$) can be used alone to monitor O_2 extraction (19). The normal $ScvO_2$ is about 65–75%, and an increase in O_2 extraction will drop the $ScvO_2$ below this range. The maximal O_2 extraction (about 50%) corresponds to an $ScvO_2$ of about 50%, and thus an $ScvO_2$ of ≤50% can be used as a marker of threatened or impaired tissue oxygenation (20).

At the other end of the spectrum, an $ScvO_2$ that is abnormally high (≥80%) is evidence of impaired tissue O_2 extraction, which is a characteristic feature of septic shock. In this situation, the $ScvO_2$ can also be fixed (i.e., does not vary with changes on O_2 delivery), and if this occurs, the $ScvO_2$ is not a reliable indicator of changes in O_2 delivery. Enter the PCO_2 gap (see next).

TABLE 14.3 Global Measures of Tissue Perfusion and Oxygenation

Measure	Critical Range	Interpretation
Cardiac Index (CI)	<2.5 L/min/m^2	Inadequate Perfusion
Oxygen Transport		
Oxygen Delivery (DO_2) Oxygen Uptake (VO_2) Oxygen Extraction (VO_2 /DO_2)	≤300 mL/min/m^2 ≤110 mL/min/m^2 ≥50% <20%	Inadequate O_2 Delivery Inadequate O_2 Utilization† Inadequate O_2 Delivery Inadequate O_2 Extraction
Central Venous O_2 Saturation ($ScvO_2$)	<50% >80%	Inadequate O_2 Delivery Inadequate O_2 Extraction
PCO_2 Gap	>6 mm Hg (>0.8 kPa)	Inadequate Perfusion
Plasma Lactate	>2 mmol/L	Inadequate O_2 Utilization†

†Present in all forms of shock.

The PCO_2 Gap

The venoarterial PCO_2 difference, also known as the PCO_2 gap, is an indirect measure of CO_2 washout from tissues (i.e., tissue perfusion). The PCO_2 gap is normally 2–5 mm Hg (0.3–0.7 kPa), and an increase in the gap to >6 mm Hg (>0.8 kPa) is evidence of tissue hypoperfusion (21). Unlike the $ScvO_2$, *the PCO_2 gap is dependent only on tissue perfusion, and it provides no information about systemic oxygenation*. The PCO_2 gap is easily obtained, and should be monitored in all patients with shock, especially those with low-flow shock (hypovolemic, cardiogenic, and obstructive shock). It can also be useful for detecting a low-flow state in septic shock, which is usually seen in advanced cases. (*Caveat:* A metabolic acidosis can increase the PCO_2 gap. This is the result of an increase in nonmetabolic CO_2 production, and it could be misinterpreted as evidence of tissue hypoperfusion. When a metabolic acidosis is present, only a normal PCO_2 gap has relevance.)

Plasma Lactate

The plasma lactate level is considered one of the most important measures in clinical shock, and has both diagnostic and prognostic applications. As mentioned earlier, a plasma lactate >2 mmol/L is considered evidence of inadequate cellular O_2 utilization, in the absence of conditions known to cause “aerobic hyperlactatemia” (see Table 9.5). If shock is the cause of an elevated

lactate level, then failure to normalize the level within 24 hours has negative implications for a satisfactory outcome (see Figure 9.4). (The plasma lactate level is described in detail in Chapter 9.)

GENERAL MANAGEMENT

The management of clinical shock has two components: treating the condition responsible for the shock, and generalized hemodynamic management. The latter component is the focus here.

Volume Resuscitation

The infusion of intravenous fluids is the very first step in the management of shock, regardless of the type of shock. (This may seem counterproductive in cardiogenic shock, but cardiac filling pressures are often suboptimal in acute heart failure, especially when it involves the right side of the heart.) Crystalloid fluids are preferred, even though about 75% of infused crystalloid fluids expand the interstitial volume, not the plasma volume (see Chapter 11).

Infused Volume

The initial infusion volume can depend on several variables (e.g., type of shock, type of patient). For the most common shock syndrome (septic shock), the recommended resuscitation volume is ≥30 mL/kg, using *ideal body weight*, in the first 3 hours (22). The minimum infusion volume for a 70 kg adult would then be about 2 liters, and for a crystalloid fluid, this means about 500 mL (25%) will be added to the plasma volume, and the remaining 1.5 liters (75%) will contribute to edema formation. This increment in plasma volume represents about 15% of the plasma volume for a 70 kg adult male (whose plasma volume is about 40 mL/kg), which seems reasonable if you consider that a 15% drop in blood volume is the threshold for producing symptoms (see next chapter). However, this “one size fits all” approach may not be suitable for adults of varying body size, and for females (whose plasma volume is lower than in males). The following are some recommendations for the initial fluid resuscitation:

. The initial resuscitation volume should take into account the type of shock (if known) and the type of patient (e.g., body size and gender), and should probably should not exceed 2 liters (crystalloid fluid) over 1–2 hours.

. The immediate goal is restoration of the baseline blood pressure.

. If the blood pressure goal is not achieved and there is other evidence of circulatory compromise (e.g., low urine output, mental status change, or elevated lactate level), then infusion of a vasoconstrictor agent (vasopressor) should be initiated.

. Volume resuscitation beyond the initial period should be guided by the assessment of fluid responsiveness (described in Chapter 11).

Vasopressor Infusions

The first issue that surfaces for vasopressor infusions is the traditional recommendation that vasopressor agents should be infused through a central venous catheter (to minimize the risk of drug extravasation and tissue necrosis). This is a source of angst when the vasopressor infusion is

an immediate need and there is no indwelling central line. Fortunately, at least 16 clinical studies have shown that vasopressors can be infused safely through peripheral catheters (in the upper arm) for up to 48 hours (23), and vasopressor infusions through midline catheters have continued for 7 days without incident (24). If there is a problem securing a free-flowing peripheral catheter, then insertion of an intraosseous catheter will provide a temporary fix (see Chapter 1).

Drug Extravasation

Extravasation of a vasoconstrictor drug should be managed as follows:

. When extravasation is first evident, stop the infusion immediately, disconnect the IV line and attach it to a syringe and gently aspirate the remaining solution in the catheter and whatever extravasated fluid can be retrieved. Then remove the catheter. Do not flush the line prior to removal.

. The drug that is used in this situation is phentolamine, a long-acting alpha blocker. The dose is 5–10 mg in 10 mL isotonic saline, which is injected directly into the area of extravasation (25). If there is skin blanching (from the local vasoconstriction), it should disappear almost immediately.

. Phentolamine must be used within 12 hours of the event to be successful.

Target Blood Pressure

The consensus recommendation is that vasopressor infusions should be titrated to maintain a mean arterial pressure (MAP) of at least 65 mm Hg (2,4,22), which is the minimum pressure needed to maintain cerebral autoregulation (the process that maintains cerebral blood flow in the face of declining blood pressures) (26). The concern that a higher target pressure might be necessary in patients with longstanding hypertension has not been validated in clinical studies (27).

VASOPRESSOR AGENTS

A variety of vasopressors are available, and are used primarily in vasodilatory (septic) shock. Most are catecholamines that promote vasoconstriction by stimulating α_1-type adrenergic receptors. The vasopressors that are currently available are listed in Table 14.4, along with the dose range for each agent. These agents are given by continuous infusion (without a loading dose), starting at a low dose and titrating upward as needed. Resistance to high doses of a vasopressor usually prompts the addition of a second agent, although there is no evidence of a survival benefit from this practice (see A FINAL WORD at the end of the chapter).

Norepinephrine

Norepinephrine is the most widely used vasopressor, and is the preferred vasopressor in septic shock (22,28). Its principal action is α_1-receptor-mediated vasoconstriction, but it is also is a weak β-receptor agonist, which produces some degree of cardiac stimulation. This might explain why the vasoconstriction from norepinephrine (in the usual doses) does not impair renal function (29).

Dosing Regimen

Norepinephrine infusions are usually started at a rate of 5–10 μg/min, which is titrated upward as needed. The β-receptor stimulation can increase the cardiac output in the low-dose range (<10 μg/min), while vasoconstriction from α-receptor stimulation begins to predominate at dose rates above 10 μg/min. When the dose reaches 30 μg/min, further increases are unlikely to produce more of a vasoconstrictor response, and a second vasopressor can be added at this point.

Adverse Effects

Serious adverse events related to norepinephrine infusions include ischemic events (myocardial, cerebral, or limb ischemia) and troublesome arrhythmias (tachycardias and bradycardia). These have been reported in about 10% of patients (30), but it is possible that many of these complications are the result of the shock, and not the vasopressor.

IMMUNOSUPPRESSION: There is evidence that leukocyte activation by bacterial products (which is an important part of the immune response) is suppressed during norepinephrine infusions (31). This is attributed to the binding of norepinephrine to adrenergic receptors on the surface of leukocytes, and it raises the possibility that norepinephrine acts as an immunosuppressant, and increases the risk of infection. The clinical significance of this is unclear, but the ironic significance is quite clear, considering the popularity of norepinephrine for treating septic shock.

TABLE 14.4 Parenteral Vasopressor Agents

Agent	Dose	Comments
Norepinephrine	5–40 μg/min	The most widely used vasopressor in clinical shock
Epinephrine	0.1–0.5 μg/kg/min	Drug of choice for anaphylactic shock, and second-line agent for septic shock Promotes lactate production
Dopamine	5–50 μg/kg/min	Once popular, but hampered by undesirable cardiac stimulation
Phenylephrine	0.5–6 μg/kg/min	A pure α agonist used mostly for anesthesia-related hypotension
Vasopressin	0.01–0.04 Units/hr	Used as a second agent in cases of septic shock that are resistant to norepinephrine
Angiotensin II	0.02–0.08 μg/kg/min initially, then infuse at ≤0.04 μg/kg/min	Can promote venous thrombosis

Epinephrine

Epinephrine is a potent β-receptor agonist that produces dose-dependent increases in heart rate, stroke volume, and blood pressure (32). It has an important role in cardiopulmonary resuscitation (see Chapter 21), and in the resuscitation of anaphylactic shock (see Chapter 17), but it is a second-line vasopressor in septic shock, and is reserved for cases where hypotension is refractory

to norepinephrine.

Dosing Regimen

The recommended doses for epinephrine in cardiopulmonary resuscitation and anaphylactic shock are presented in Chapters 21 and 17, respectively. For septic shock, epinephrine is given as a continuous infusion with no loading dose, starting at 0.1 μg/kg/min and titrating upward, as needed. The maximum dose is 0.5 μg/kg/min (27).

Adverse Effects

The adverse effects of epinephrine include unwanted cardiac stimulation (i.e., tachycardia and arrhythmias), and splanchnic hypoperfusion from α-mediated vasoconstriction (33), which can damage the mucosal barrier in the bowel. Epinephrine also has undesirable metabolic effects, including an increase in metabolic rate (which is counterproductive in a shock syndrome), hyperglycemia (from α-receptor-mediated inhibition of insulin secretion), and an increase in plasma lactate levels (due to an increase in aerobic lactate production) (34). The increase in lactate levels can be misleading in shock syndromes.

Dopamine

Dopamine is an endogenous catecholamine that serves as a precursor for norepinephrine. It was once the preferred vasopressor in septic shock, but its tendency to produce troublesome tachycardia and arrhythmias led to a fall from grace. Dopamine has a variety of dose-dependent effects (35):

. At low infusion rates (≤3 μg/kg/min), dopamine selectively activates dopamine-specific receptors in the renal and splanchnic circulations, resulting in increased blood flow in these regions.

. At moderate infusion rates (3–10 μg/kg/min), dopamine stimulates β-receptors in the heart and peripheral circulation, producing an increase in cardiac stroke output.

. At high infusion rates (>10 μg/kg/min), dopamine produces a dose-dependent activation of α-receptors in the peripheral circulation, resulting in progressive vasoconstriction and an increase in systemic vascular resistance. This vasopressor effect increases ventricular afterload, and can reverse the stroke volume augmentation produced by lower doses of dopamine.

Dosing Regimen

Dopamine is usually started at a dose of 5 μg/kg/min, and is titrated upward as needed. A dose of 5–10 μg/kg/min will usually increase the cardiac output, but a higher dose (>10 μg/kg/min) may be needed to increase the blood pressure. The benefits of dopamine are usually seen at dose rates of 5–20 μg/kg/min, but dose rates of 50 μg/kg/min and even higher have been reported (35).

Adverse Effects

The major risk with dopamine is tachycardia and troublesome tachyarrhythmias (e.g., atrial fibrillation), which occur more frequently with dopamine than with the other vasopressors (36). As mentioned, this risk has resulted in a marked decline in the popularity of dopamine for both cardiogenic and septic shock. Another risk with dopamine that deserves mention is increased

intraocular pressure, which has been reported at low dose rates (1–4 μg/kg/min) (37).

Phenylephrine

Phenylephrine in a pure α-receptor agonist that produces widespread vasoconstriction, which can be accompanied by bradycardia, a decrease in cardiac stroke output (usually in patients with cardiac dysfunction), and hypoperfusion of the kidneys and bowel. The principal use of phenylephrine is for hypotension produced by anesthesia (spinal or general), where it is often given in bolus doses. Phenylephrine is not recommended for any of the shock syndromes (22,38), although a clinical study comparing phenylephrine and norepinephrine in septic shock showed no difference in hemodynamic effects or clinical outcomes with either drug (39). In the ICU, phenylephrine is useful for managing septic shock in patients with rapid atrial fibrillation (author's observation).

Dosing Regimens

. For treating hypotension during anesthesia, phenylephrine can be given as a bolus dose of 50–100 μg, which can be repeated once after a few minutes, if needed. If the hypotension is not relieved, then a continuous infusion of the drug is recommended, starting at a dose rate of 10–35 μg/min and titrating upward. The maximum recommended dose is 200 μg/min (38).

. For managing septic shock, phenylephrine is given as a continuous infusion with no initial bolus dose, starting at a dose of 0.5 μg/kg/min, and titrating upwards as needed. Dose rates above 6 μg/kg/min are unlikely to produce any further benefit (38).

Vasopressin

Vasopressin, also known as antidiuretic hormone, produces vasoconstriction as a result of specialized vasopressin (V_1) receptors on vascular smooth muscle. Vasoconstriction is most prominent in skin, skeletal muscle, and splanchnic circulations (39). Vasopressin does not increase blood pressure in healthy volunteers, but it can produce significant increases in blood pressure in patients with vasodilatory shock (40). Other actions of vasopressin include enhanced water reabsorption in the distal renal tubules (mediated by V_2 receptors), and stimulation of ACTH release by the anterior pituitary gland (mediated by V_3 receptors).

Use as a Vasopressor

Vasopressin can be used in the following clinical situations.

. In the resuscitation of cardiac arrest, vasopressin can be given as a single IV dose (40 units) to replace the first or second dose of epinephrine.

. In cases of septic shock that are resistant to hemodynamic support with norepinephrine (usually defined as norepinephrine dose of ≥0.2 μg/kg/min without an adequate blood pressure), the addition of vasopressin is recommended (22), as this can raise the blood pressure and reduce the catecholamine requirement (catecholamine sparing effect). However, the addition of vasopressin has *no proven survival benefit* (41).

Dosing Regimen

For septic shock, vasopressin is given as a continuous infusion at 0.03–0.04 Units/hr. This dose rate is not titrated (unlike the catecholamine vasopressors). The adverse effects of vasopressin are similar in type and frequency to those mentioned previously for norepinephrine (30).

Angiotensin II

Angiotensin II is a synthetic analogue of human angiotensin that acts on vascular smooth muscle to promote systemic vasoconstriction, and it also stimulates vasopressin release from the posterior pituitary gland. It was approved for use in vasodilatory shock in 2018, and has been used primarily in cases of norepinephrine resistance. It has raised the blood pressure in as many as 67% of cases (42), but the impact on mortality rates has been inconsistent (42,43).

Dosing Regimen

Angiotensin II is given by continuous intravenous infusion: the initial dose is 20 ng/kg/min (0.02 μg/kg/min), which can be increased every 10–15 minutes if needed, to 80 ng/kg/min (0.08 μg/kg/min) in the first 3 hours (44). Thereafter, the maintenance dose should not exceed 40 ng/kg/min (0.04 μg/kg/min). There is no dose adjustment for hepatic or renal dysfunction.

Adverse Effects

The major risk with angiotensin II is venous thrombosis. Angiotensin stimulates the release of plasminogen activator inhibitor-1 from vascular smooth muscle, which blocks fibrinolysis, and it also increases platelet adhesion. In one clinical trial, the incidence of thrombotic events with angiotensin II was more than double the incidence with placebo (13% vs. 5%, respectively) (44).

Midodrine

Midodrine is an orally administered α-receptor agonist that was FDA-approved in 1996 for the treatment of orthostatic hypotension. The clinical experience with midodrine in the ICU is summarized below.

. Midodrine has proven effective for limiting or preventing hypotension during hemodialysis (45). The effective dose varies from 5 mg to 20 mg, given 20–30 minutes before dialysis. An additional smaller dose can be given during the dialysis if needed.

. Adjuvant treatment with midodrine (20 mg every 8 hours) does not hasten the discontinuation of parenteral vasopressor therapy (46,47).

Despite its appeal as a vasopressor that is easy to administer, midodrine offers no advantage for the management of shock.

GOALS OF RESUSCITATION

The goals of resuscitation for clinical shock have been mentioned throughout this chapter, and are briefly summarized here. The goals can be grouped into two categories, tissue perfusion and oxygen transport, as shown in Table 14.5.

Tissue Perfusion

The importance of blood flow in shock is readily apparent when you consider that three of the four types of shock (i.e., hypovolemic, cardiogenic, and obstructive) are low-flow conditions. One of the very first goals in shock resuscitation is to obtain accurate measurements of the mean arterial pressure (MAP), which is the pressure that drives peripheral flow. This requires direct intra-arterial pressure recordings from an arterial catheter. Once this is achieved the MAP should be maintained at ≥65 mm Hg. Do not monitor the systolic pressure (if possible), since this is a reflected pressure wave that is traveling back to the heart (i.e., away from the periphery). Remember that flow in the microcirculation is laminar, not pulsatile, and has no systolic and diastolic components.

Monitoring the cardiac output with pulmonary artery (PA) catheters was once a staple of critical care management, but this practice took a nosedive about 25 years ago because of evidence that PA catheters do not improve survival in critically ill patients. (A harsh judgement, since the catheter is a monitoring device, not a therapy.) If a cardiac output measurement is available, the goal is to keep the size-adjusted output (the cardiac index) above 2.5 L/min/m^2.

An assessment of tissue perfusion is also possible using the PCO_2 gap, which is a measure of CO_2 washout from tissues. A PCO_2 gap that is <6 mm Hg is considered evidence of adequate tissue perfusion. This measure is easily obtained, and should be monitored in all patients with shock, even when the cardiac output measurement is available (since microcirculatory flow can be sluggish when the global cardiac output is in the normal range). *Caveat:* Metabolic acidosis can increase the nonmetabolic production of CO_2, and this can result in a spurious increase in the PCO_2 gap.

Finally, tissue perfusion can be assessed by monitoring organ function, and urine output is appropriate for this purpose because a decrease in urine output is often one of the earliest signs of impending shock. Since oliguria is identified by a urine output <0.5 mL/kg/hr, the goal of resuscitation is to exceed this threshold. Mental status can also be monitored, but it is not as easy to quantify as urine output.

TABLE 14.5 Goals of Resuscitation for Shock

Category	Goals
Tissue Perfusion	MAP ≥65 mm Hg CI ≥2.5 L/min/m^2 PCO_2 Gap <6 mm Hg Urine Output >0.5 mL/kg/hr
Oxygen Transport	DO_2 >300 mL/min/m^2. VO_2 >110 mL/min/m^2 O_2 Extraction <50% $ScvO_2$ >50% Lactate <2 mmol/L

Oxygen Transport

Monitoring the O_2 transport variables has obvious implications because a derangement on one of these variables is responsible for clinical shock.

- Three of the major shock syndromes (i.e., hypovolemic, cardiogenic, and obstructive shock) are the result of inadequate O_2 delivery to tissues, usually from an inadequate cardiac output, with a contribution from a low hemoglobin level in one case (hemorrhagic shock). The goal in these cases is a cardiac index (CI) >2.5 L/min/m^2, an O_2 delivery (DO_2) >300 mL/min/m^2, and an O_2 uptake (VO_2) >110 mL/min/m^2. If these variables are not monitored (which happens in most cases), then the goal of resuscitation is a central venous O_2 saturation ($ScvO_2$) >50% and a plasma lactate level <2 mmol/L.
- *Septic shock is NOT the result of inadequate O_2 delivery, but instead is the result of a defect in oxidative phosphorylation in dysfunctional mitochondria* (48,49). This condition is known as *cytopathic hypoxia* (48), and it can be associated with a defect in O_2 extraction from capillary blood. The goals of management in this case include an O_2 extraction <80%, and an O_2 uptake (VO_2) >110 mL/min/m^2. (The $ScvO_2$ may not be reliable in sepsis, as a result of the defective O_2 extraction.) If these variables are not monitored, the goal of resuscitation is simply a normal plasma lactate level. (The management of septic shock is presented in detail in Chapter 17.)
- The universal goal of resuscitation in all forms of shock is normalization of the plasma lactate level (<2 mmol/L).

Of course, the tacit goal of resuscitation in clinical shock is survival.

A FINAL WORD

Hypotension as a Consequence, not a Cause, of Shock

The resuscitation of shock is dominated by the desire to raise the blood pressure, which is based on the assumption that the low blood pressure is responsible for the shock. The following observations create some doubt about this approach.

- Shock is defined as a derangement in cellular O_2 utilization (2), not a derangement in blood pressure.
- Relieving hypotension has been the major focus of shock management for over 70 years (since norepinephrine was introduced for clinical use in 1950), yet the mortality rate in shock remains unacceptably high, and the use of two and even three vasopressors offers no survival benefit (50).
- Low blood pressures occur in conditions other than shock (e.g., autonomic neuropathies, adrenal insufficiency, 5% of healthy adults), and they do produce anoxic organ injury or elevated lactate levels. In fact, low blood pressures have proven beneficial in penetrating injuries by limiting blood loss (see the next chapter).

One possible explanation for these observations is that *hypotension does not cause shock, but instead is a consequence of shock.* Shock is well known for causing multiorgan dysfunction, and

one of the dysfunctional organs could be the blood vessels. If this is the case, then correcting the blood pressure will not correct the shock (or improve survival), just like hemodialysis for shock-related renal failure will not correct the shock (or improve survival).

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Chapter 15

Hemorrhagic Shock

It is a bad sign in acute illnesses when the extremities become cold.

Hippocrates *Aphorisms,* 400 B.C.

Trauma is the leading cause of death globally in the 25–49 year age group (1), and the most treatable cause of death in these cases is hemorrhagic shock. The resuscitation of traumatic blood loss presents many challenges (as described in this chapter), and one of these is the design of the circulatory system, which operates with a limited volume and a volume-sensitive stroke pump. This is an energy-efficient design that limits the workload of the heart, but it creates an intolerance to blood loss; e.g., whereas the lungs, liver, and kidneys can lose as much as 75% of their functional mass without a fatal outcome, loss of as little as 30% of the (limited) blood volume can be fatal. This intolerance to blood loss is the dominant concern in the bleeding patient.

This chapter describes the physiology and classification of acute blood loss, and presents the relevant features and strategies involved in the resuscitation of hemorrhagic shock, with an emphasis on life-threatening blood loss from traumatic injuries.

ACUTE BLOOD LOSS

The normal blood volume in adults is estimated at 66 mL/kg (lean body weight) for males, and 60 mL/kg for females (2). For an adult male with a lean body weight of 75 kg (165 lbs), the estimated blood volume is 66 × 75 = 5 liters, while an adult female with a lean body weight of 60 kg (132 lbs) has an estimated blood volume of 60 × 60 = 3.6 liters.

Compensatory Responses

Acute blood loss triggers the following compensatory responses, which help to mitigate the adverse consequences of the volume loss (3,4).

. The decrease in blood pressure promotes the movement of interstitial fluid into the bloodstream. This *transcapillary refill* can add as much as one liter to the plasma volume, but it leaves an interstitial fluid deficit.

. There is a physiological stress response that involves activation of the sympathetic nervous system, which promotes tachycardia and peripheral vasoconstriction, both aimed at preserving tissue perfusion.

. The stress response also stimulates the release of antidiuretic hormone (ADH) from the posterior pituitary gland, which counteracts the volume loss by promoting the renal retention of water.

. The decrease in renal perfusion activates the renin–angiotensin–aldosterone system. Angiotensin promotes widespread vasoconstriction, which helps to support tissue perfusion pressure, while aldosterone promotes renal sodium retention, which provides support for the extracellular volume.

Progressive Blood Loss

Acute blood loss can be described with the following classification system (5), which is also outined in Table 15.1.

TABLE 15.1 Classification System for Acute Blood Loss

	Class I	Class II	Class III	Class IV
Volume Deficit	<15%	15–30%	31–40%	>40%
Volume Loss	<10 mL/kg	10–20 mL/kg	21–30 mL/kg	>30 mL/kg
Heart Rate	↔	↑	↑↑	↑↑ / ↓
Blood Pressure	↔	↔ / ↓	↓	↓↓
Urine Output	↔	↔ / ↓	↓	↓↓
Plasma Lactate	↔	↔	↑	↑↑
Interpretation	Asymptomatic Phase	Compensated Phase	Shock Phase	Advanced Shock
Resuscitation	None	Crystalloid Fluids	Blood	Massive Transfusion

Adapted from Reference 5.

CLASS I: Loss of <15% of the blood volume (or <10 mL/kg). The volume loss in this case (which is typically less than one liter) is fully restored by transcapillary refill, so blood volume is maintained, clinical findings are minimal or absent, and volume resuscitation is not necessary (3).

CLASS II: Loss of 15–30% of the blood volume (or 10–20 mL/kg). This represents the compensated phase of hypovolemia, where blood pressure is maintained by systemic vasoconstriction (4). Urine output may begin to fall, but does not reach the level of oliguria (<0.5 mL/kg/hr). The vasoconstrictor response is most intense in the splanchnic circulation, and splanchnic hypoperfusion can lead to disruption of the intestinal mucosa and invasion of the bloodstream with enteric pathogens (6).

CLASS III: Loss of 31–40% of the blood volume (or 21–30 mL/kg). This marks the onset of decompensated blood loss or *hemorrhagic shock*, where the vasoconstrictor response is no longer able to sustain blood pressure and organ perfusion. The clinical consequences can include supine hypotension, signs of impaired organ perfusion (oliguria, altered mentation, cool extremities) and evidence of anaerobic metabolism (i.e., lactate accumulation in blood).

CLASS IV: Loss of >40% of blood volume (or >30 mL/kg). This degree of blood loss results in profound hemorrhagic shock, which may be irreversible. Clinical manifestations include multiorgan failure and severe metabolic (lactic) acidosis. This category includes *massive blood loss*, which is described later in the chapter.

Hemoglobin and Hematocrit

The use of the hemoglobin concentration and hematocrit (H & H) to evaluate the presence and severity of acute blood loss is both common and inappropriate. Changes in hematocrit show a poor correlation with blood volume deficits and erythrocyte deficits in acute hemorrhage (7), and the reason for this discrepancy is demonstrated in Figure 15.1. Acute blood loss involves the loss of whole blood, which results in proportional decreases in the volume of plasma and erythrocytes. As a result, acute blood loss results in a decrease in blood volume, but not a decrease in the H & H. The H & H will eventually decline as a result of transcapillary refill, and the compensatory increase in antidiuretic hormone and aldosterone activity mentioned previously, but this effect is not apparent for 8–12 hours, and it can take a few days to become fully established.

The right side of Figure 15.1 shows how the resuscitation fluid influences the hematocrit. Infusion of isotonic saline increases the plasma volume but not the red cell volume, resulting in a dilutional decrease in the hematocrit (8). On the other hand, resuscitation with whole blood adds to both plasma and red cell volumes proportionally, so there is no change in hematocrit. These examples demonstrate that *in the early hours after acute blood loss, the hemoglobin and hematocrit are reflections of the resuscitation effort* (the type and volume of fluids infused), *and not the extent of blood loss*.

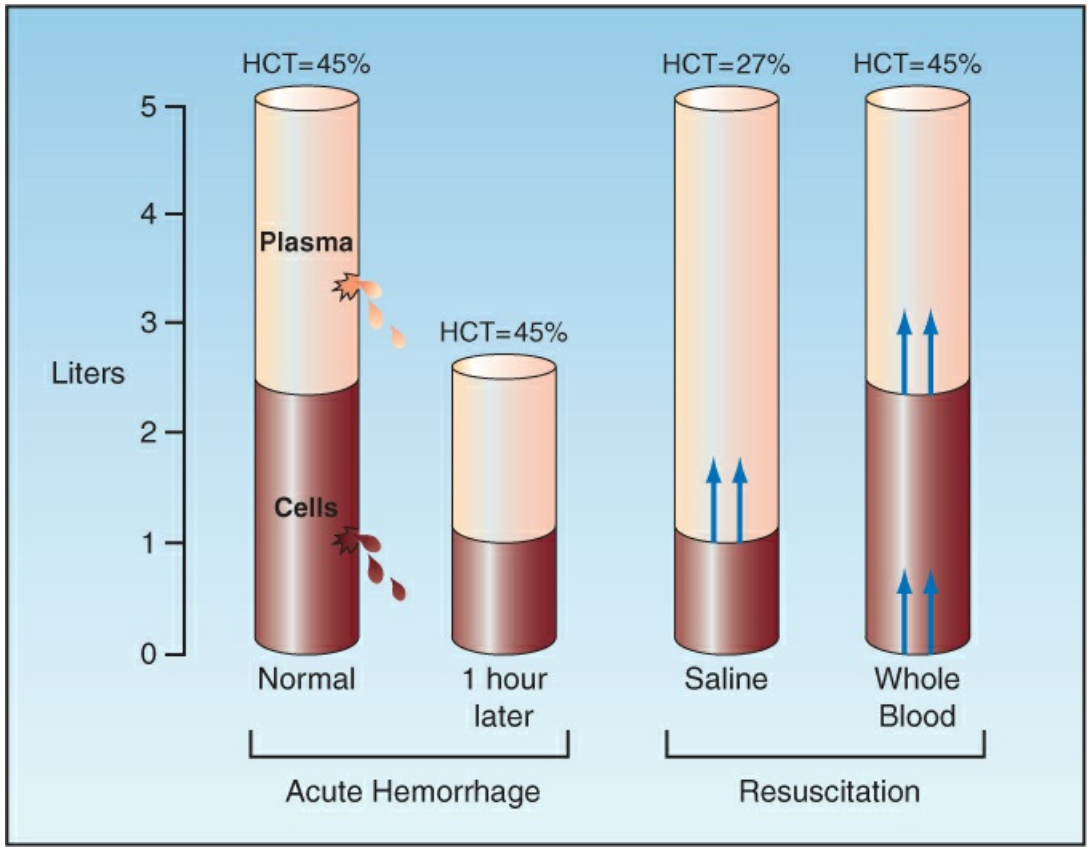

FIGURE 15.1 Influence of acute hemorrhage and fluid resuscitation on blood volume and hematocrit. See text for explanation.

RESUSCITATION BASICS

The Catheters

The determinants of flow through vascular catheters are described in Chapter 1 using the Hagen-Poiseuille equation, which is shown below (9).

$$Q = \Delta P \times (\pi r^4 / 8 \mu L) \qquad (15.1)$$

This equation states that the steady or laminar flow (Q) in a rigid tube (catheter) is directly related to the pressure gradient along the tube (ΔP = Pin – Pout) and the fourth power of the radius of the tube (r^4), and is inversely related to the length of the tube (L) and the viscosity of the fluid (μ). These relationships indicate that *short, large-bore peripheral vein catheters are much better suited for rapid infusions than the longer central venous catheters*. This is demonstrated in Figure 15.2, which shows that for a given gauge size, the gravity-driven flow of water through a 1.2-inch peripheral vein catheter is about 5 times greater than the flow through an 8-inch central venous catheter. Also note that increasing the bore size of a catheter from 18 gauge to 16 gauge results in a two-fold increase in flow rate.

Rapid Infusion Catheters

Very large bore peripheral catheters are available in 7 French and 9 French sizes (equivalent to 13 gauge and 11 gauge sizes, respectively) and are about 2 inches in length. These *rapid infusion catheters* are typically used with pressurized infusion systems (see later), and they can deliver up to one liter per minute (10).

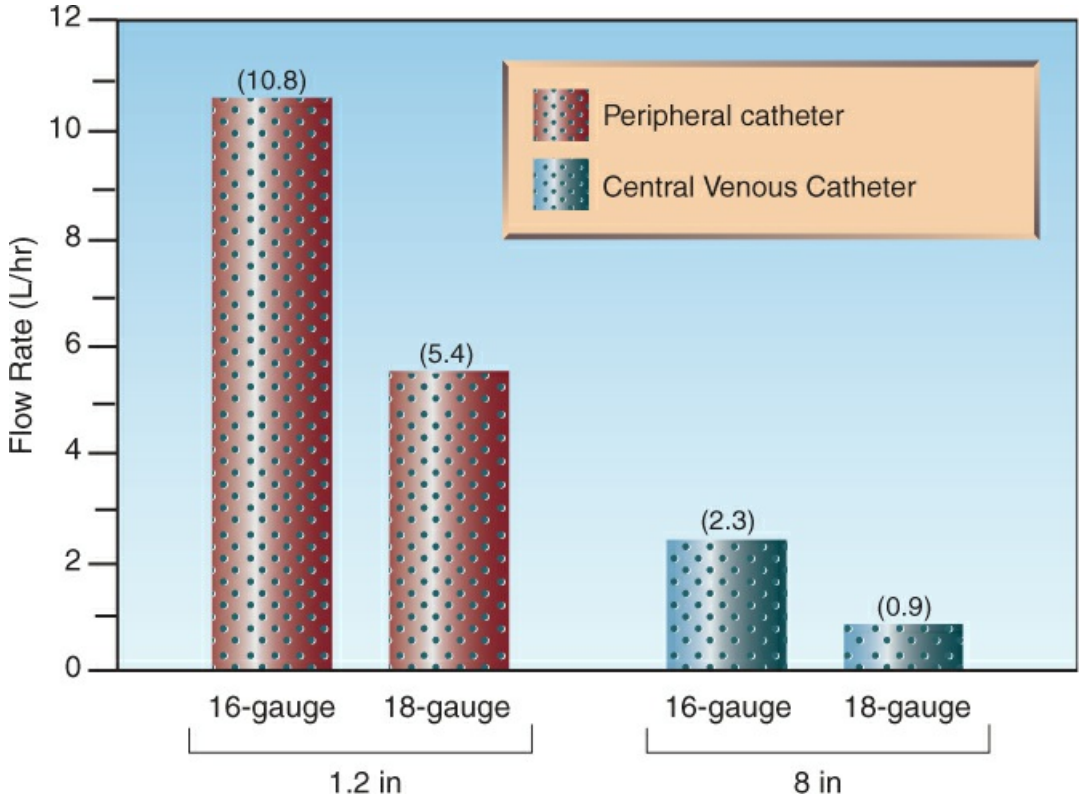

FIGURE 15.2 The influence of catheter dimensions on the gravity-driven flow of water. Data from www.emnote.org (for peripheral catheters) and www.teleflex.com (for central venous catheters).

Introducer Catheters

Large-bore introducer catheters are used as conduits for multilumen catheters (see Figure 8.1), but they can also be used as stand-alone infusion devices. They are available in 8.5 French and 9 French sizes (equivalent to about 11 gauge), and can deliver up to one liter per minute when used with pressurized infusion systems (10). These catheters are about 10 cm (4 inches) in length, and are inserted into large central veins (which make them less appealing than the rapid infusion catheters). Some introducer catheters have an additional side infusion port (see Figure 8.1), but the flow capacity of this port is only 25% of the flow capacity of the catheter (11), so it should be bypassed for rapid infusion rates.

Resuscitation Fluids

The different types of resuscitation fluids for acute blood loss are shown in Table 15.2. Each of these fluids (except whole blood) has been described in detail elsewhere in the book, and the following is only a brief summation.

TABLE 15.2	Resuscitation Fluids for Blood Loss	
Type of Fluid	**Products**	**Principal Effect**
Colloid Fluid	Albumin (5%, 25%), Hydroxyethyl Starches, Dextrans	Expands the plasma volume
Crystalloid Fluid	Isotonic Saline, Ringer's lactate, Normosol, Plasma-Lyte	Expands the extracellular volume
RBC Concentrate	Packed RBCs	Increases the O_2 content of blood
Plasma	Fresh Frozen Plasma, Liquid Plasma	Provides procoagulant proteins
Plasma Precipitate	Cryoprecipitate, Fibrinogen Concentrate	Increases fibrinogen levels
Platelet Concentrate	Multiple-Donor Platelets, Single-Donor Platelets	Increases circulating platelets
Whole Blood	Type-Specific Blood Group O Blood	All of the above

Asanguinous Fluids

Asanguinous fluids (colloids and crystalloids) are used in the resuscitation of moderate (Class II) blood loss, and in the initial stage of resuscitation for hemorrhagic shock. Colloid fluids are much more effective for promoting the cardiac output (see Figure 15.3), because they expand the plasma volume more than crystalloid fluids, as explained in Chapter 10. However, despite the superiority of colloid fluids for expanding the plasma volume, crystalloid fluids have been the preferred fluid for the resuscitation of acute blood loss (see next).

CRYSTALLOIDS AND BLOOD LOSS: The perceived value of crystalloid fluids in hemorrhagic shock can be traced back to experimental studies in the 1960s. Using an animal model of hemorrhagic shock, these studies showed that few animals survived when shed blood, or shed blood plus plasma, was reinfused, but survival markedly improved when a crystalloid fluid (Ringer's lactate) was added to shed blood replacement (13). These same studies also showed that there was a disproportionate (40%) decrease in the volume of interstitial fluid in hemorrhagic shock, and further, that this volume was restored only when the crystalloid fluid was added to the shed blood replacement. These observations implied that an interstitial fluid deficit was a critical factor in the inability to survive hemorrhagic shock, and the crystalloid fluid resuscitation was needed to correct this deficit (and improve survival).

The consensus view at the present time is that fatal outcomes in hemorrhagic shock are the result of persistent bleeding and an unrelenting coagulopathy (described later in the chapter), and that the aggressive use of crystalloid fluids can aggravate ongoing blood loss by promoting a dilutional decrease in coagulation factors. As a result, the current emphasis is on limiting the use

of crystalloid fluids in the resuscitation of life-threatening hemorrhage (see "damage control resuscitation" later in the chapter).

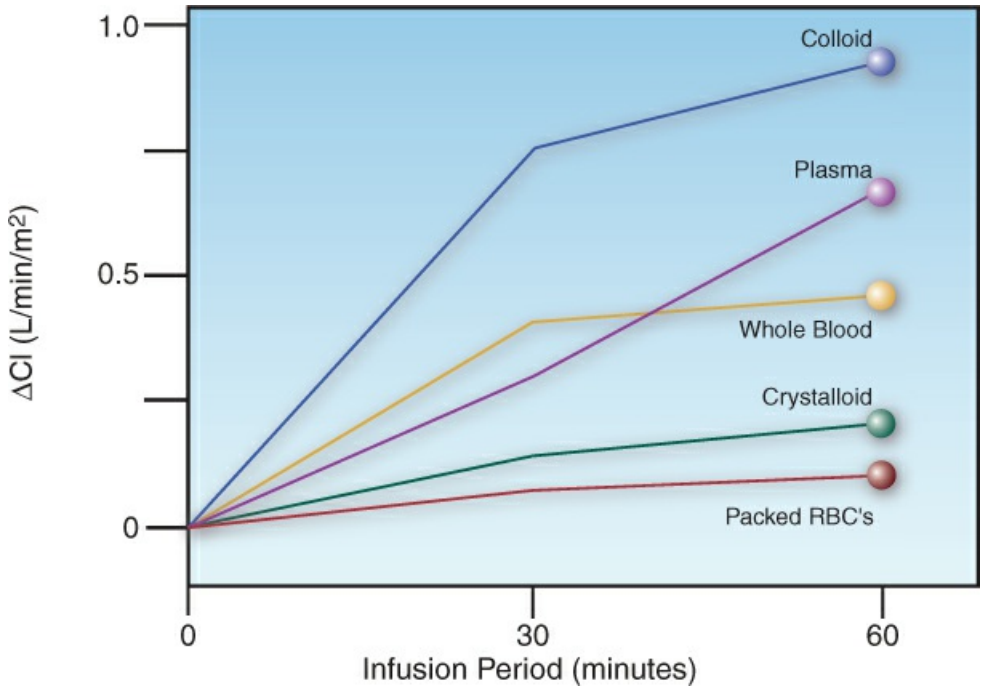

FIGURE 15.3 The influence of a one-hour infusion of selected resuscitation fluids on the cardiac index (CI). The colloid is 10% dextran-40, and the crystalloid is Ringer's lactate. Infusion volumes are roughly equivalent (500 mL), except for the crystalloid (1 liter). Data from Reference 12.

Erythrocyte Concentrates

Erythrocyte concentrates, better known as "packed red blood cells" are produced by centrifugation of donor blood. Each unit has a hematocrit of about 60% and a volume of about 350 mL (see Table 12.3). Packed RBCs do not promote cardiac output (see Figure 15.3) because of their high viscosity, and they are used only to increase the oxygen carrying capacity of blood. (See Chapter 12 for more on packed RBCs.)

Plasma Products

Plasma is stored at −18° C (–0.4° F), and must be thawed before using. This "fresh frozen plasma" (FFP) is available in aliquots (units) of about 230 mL, and is used as a source of coagulation factors, and as a volume expander in massive transfusion protocols (see later). FFP has two disadvantages: i.e., the time required for thawing can lead to delays in resuscitation, and there is a limited shelf life after thawing, which can lead to wastage. These disadvantages are not shared by *liquid plasma*, which is not frozen, and can be stored at 34°–43° F for up to 26 days. Liquid plasma has proven equivalent in efficacy to FFP while also reducing wastage (14). (See Chapter 13 for more on plasma transfusions.)

Cryoprecipitate

Cryoprecipitate is a frozen plasma precipitate that is rich in fibrinogen and Factor VIII. It has a

volume of about 10–15 mL, and is used to raise plasma fibrinogen levels (15). Cryoprecipitate has the same disadvantages as FFP: i.e., must be thawed before use, and has a limited shelf life after thawing. Other disadvantages include a variable fibrinogen content, and an increased risk of transmitted infections. These problems are not shared by *fibrinogen concentrates*, which have a consistent fibrinogen content (20 g/L), do not require thawing, and have no risk of transmitted infections (16).

Whole Blood

Whole blood is considered the ideal replacement fluid for acute blood loss, and it can be stored at 1°–6° C (34°–43° F) for up to 35 days (17). However, whole blood is not readily available, because of the standard practice of separating donor blood into its components, which optimizes its utilization.

Fresh whole blood has been used during the recent military conflicts in the Middle East, which was made possible by the use of "walking blood banks" (i.e., fellow soldiers), and it showed a survival benefit when compared to component therapy (17). As a result of this experience, cold-stored whole blood has been evaluated in a civilian setting, but it has not shown the same survival benefit as it did in the military studies (18,19). However, there is evidence of a survival benefit when whole blood is combined with component therapy (19), and it may be that whole blood will fill the gap when there is a limited supply of blood components.

LOW-TITER GROUP O BLOOD: Group O blood is considered universal donor blood, and is used when type-specific blood is not immediately available. However, transfusion reactions have occurred with Group O blood that has exceptionally high titers of anti-A and anti-B antibodies (20). "Low-titer" Group O blood has low levels of anti-A and anti-B antibodies, and is considered a safer alternative to Group O blood. The experience with low-titer Group O blood has been similar to whole blood; i.e., a survival benefit has been demonstrated in military studies, but not in the civilian population (21).

Rapid Infusion Systems

Rapid blood replacement is often necessary in massive hemorrhage, and rapid infusion systems are available that can deliver warmed blood products at rates up to 1 liter per minute (22). These systems use a roller pump to create pressures up to 300 mm Hg to deliver a preselected infusion rate. Heating coils are also used to deliver the infusate at body temperature, which eliminates the risk of hypothermia from infusing room-temperature fluids.

Pressurized infusion systems are especially helpful in transfusing erythrocyte concentrates (packed RBCs), which are highly viscous and do not flow readily. This is demonstrated in Table 15.3, which shows that the gravity-driven infusion of packed RBCs is sluggish, and is improved by dilution with saline (23). However, rates of blood replacement can be 5 L/hr (83 mL/min) or higher in life-threatening hemorrhage, and these rates can only be reached with pressurized infusions. Concerns about hemolysis with rapid infusion systems have not been validated (24).

TABLE 15.3 Infusion of Packed RBCs: Influence of Dilution, Pressure, and Catheter Size

	Maximum Flow (mL/min)		
	18 ga	16 ga	7 Fr RIC
	1.2 in	1.2 in	2.0 in
1 Unit PRBCs – No Dilution Gravity-Driven Flow	5	7	—
1 Unit PRBCs + 100 mL Saline Gravity-Driven Flow	39	49	—
1 Unit PRBCs + 1 Unit FFP Pressurized Flow (300 mm Hg)	183	448	1,000

Data from References 24 and 25. RIC = Rapid infusion catheter.

RESUSCITATION STRATEGIES

There are two fundamental goals in the bleeding patient. The first goal is to support the delivery of oxygen to tissues by promoting cardiac output and maintaining an adequate hemoglobin concentration. The second (and equally important) goal is "source control" to stop the bleeding, as continued bleeding not only depletes resources, it increases the risk of a life-threatening coagulopathy (see later).

TABLE 15.4 Asanguinous Resuscitation Volumes for Class II Hemorrhage

Steps	Methods
1. Estimate normal plasma volume (PV)	PV = 40 mL/kg (males)* = 36 mL/kg (females)
2. Estimate % loss of plasma volume	Class II: 15–30% Loss
3. Calculate plasma volume deficit (PVD)	PVD = PV x % Loss
4. Estimate resuscitation volume (RV)	RV = PVD x 1 (colloids) = PVD x 3 (crystalloids)

* Estimated plasma volumes from Reference 2.

Hemorrhage Without Shock

Blood loss that is accompanied by a decrease in blood pressure or urine output, but without evidence of shock (e.g., plasma lactate is not elevated) can be managed initially with asanguinous fluids. (This is equivalent to Class II blood loss presented earlier.) The resuscitation volume can be estimated as shown in Table 15.4. Note that the volume for crystalloid fluids is 3 times the estimated loss of plasma volume, which is a conservative estimate (since only 20–25% of crystalloid fluids expand the plasma volume).

When the plasma volume is repleted, packed RBCs may be needed to attain a target Hb of 7–8 g/dL (see Chapter 12), FFP may be needed if the INR is >1.5 (25), and platelet transfusions are indicated if the platelet count falls below 50,000/μL (see Chapter 13). If bleeding continues, then the resuscitation strategy described next should be considered.

Hemorrhagic Shock

The resuscitation of hemorrhagic shock described here follows the principles of "damage control resuscitation" (26), which is typically used for massive blood loss (e.g., infusion of 4 units of RBCs in one hour), but will benefit all cases of life-threatening hemorrhage. The basic tenets of damage control resuscitation include timely source control, permissive hypotension, restricting the infusion of crystalloid fluids, and resuscitation with whole blood, or its equivalent in component therapy.

Permissive Hypotension

The impetus for permissive hypotension comes from studies of trauma-related hemorrhage, which have shown that aggressive fluid resuscitation can exacerbate bleeding before the hemorrhage is controlled (27). This led to an emphasis on reducing fluid resuscitation to allow blood pressures to remain lower than normal (e.g., systolic BP 80–90 mm Hg or mean BP of 50 mm Hg) until the bleeding is controlled. This strategy has been shown to reduce transfusion requirements and the risk of a dilutional coagulopathy (28,29), but the effect on mortality rates has been inconsistent (27–29). The major issue with this strategy is ensuring that the low blood pressure is not promoting dangerous tissue hypoperfusion, so monitoring plasma lactate levels and markers of organ perfusion, such as urine output, is essential (as it should be in all cases of hemorrhagic shock).

Coagulopathy

One of the principal fears in the bleeding patient is persistent blood loss, which can be the result of inadequate source control and/or a coagulopathy. The latter process is often the result of acidosis (which inhibits coagulation factors at a pH <7.2), hypothermia (which decreases platelet adherence), or the infusion of asanguinous fluids (which has a dilutional effect on coagulation factors) (30). However trauma victims can have a coagulopathy that is independent of the traditional sources, and this "trauma-induced coagulopathy" (TIC) has a negative impact on outcomes. Studies of combat casualties in the Middle East showed that TIC was present on admission in 40% of the cases, and the presence of TIC created a 6-fold increase in the mortality rate (31).

The major culprit in TIC is activation of protein C as a result of endothelial injury (27). The activated protein C not only deactivates factors V and VIII (which inhibits clot formation), it also triggers fibrinolysis (which promotes clot dissolution, and leads to a consumptive decrease in fibrinogen levels) (30). Platelet dysfunction may also play a role in TIC (32).

Hemostatic Resuscitation

The basic elements of hemostatic resuscitation are outlined in Figure 15.4 (33). The most important element is the infusion of RBCs, plasma, and platelets in proportions that mimic whole blood replacement. This 1:1:1 replacement strategy can be achieved by infusing one unit of FFP for every unit of packed RBCs, and adding one platelet pack (multidonor or single-donor platelets) for every 5 units of PRBCs and FFP. (Remember that platelet transfusions are equivalent to the platelets from 5–6 donors.) This approach not only optimizes the replacement of clotting elements (coagulation factors and platelets), it also minimizes the risk of a dilutional coagulopathy from the infusion of crystalloid fluids. Infusions should be warmed to body temperature to avoid hypothermia.

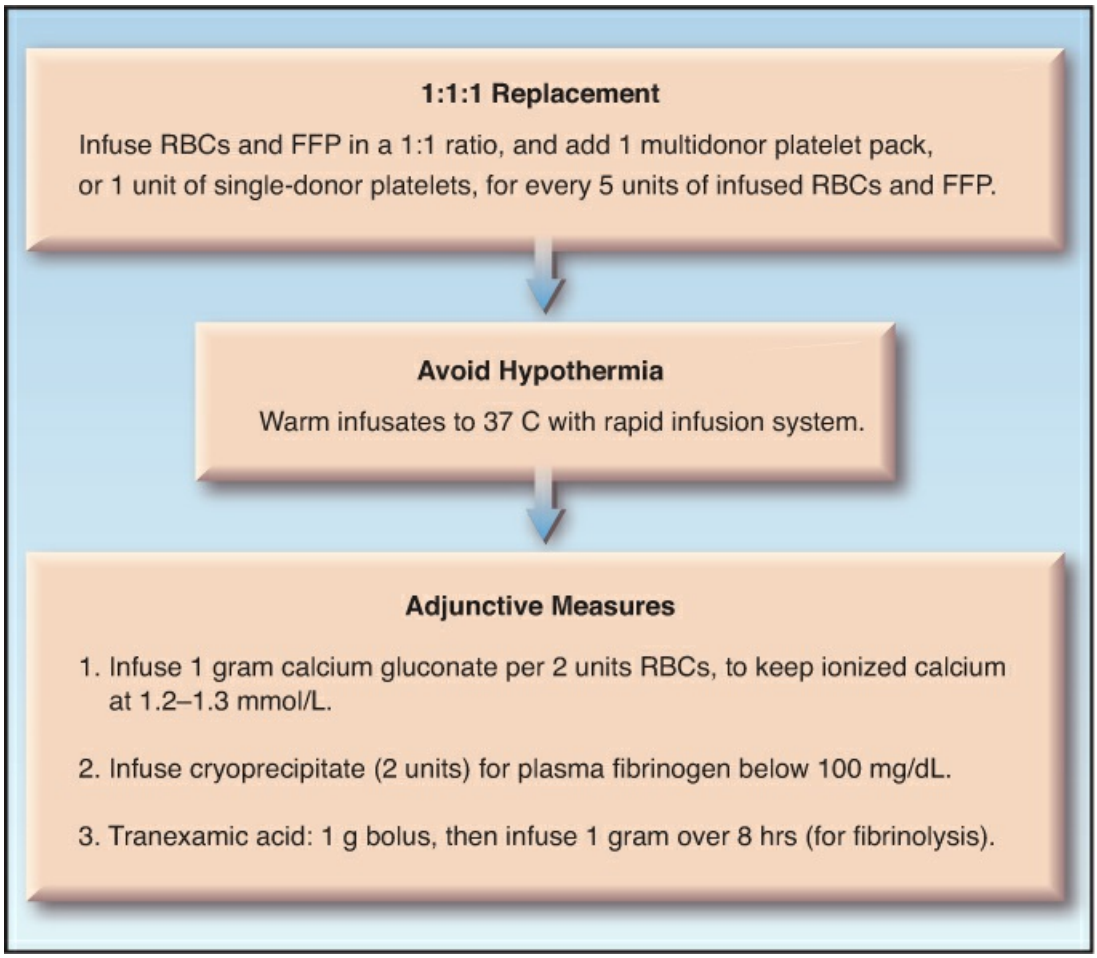

FIGURE 15.4 The principal components of hemostatic resuscitation. See text for explanation.

ADJUNCTIVE MEASURES: Other measures that promote hemostasis include calcium supplementation to maintain an ionized calcium of 1.2–1.3 mmol/L (4.6–6 mg/dL), cryoprecipitate (two units) for a plasma fibrinogen level <100 mg/dL, and empiric treatment for fibrinolysis with tranexamic acid (1 gram IV as a bolus dose, followed by infusion of 1 gram over 8 hours) (33).

END-POINTS: The end-points of hemostatic resuscitation include a plasma fibrinogen level >100 mg/dL, an INR <1.5, an activated PTT <1.5 times normal, and a platelet count of ≥100,000/μL (30). However, these conventional measures are not well suited for detecting the hemostatic defects in TIC, and "viscoelastic assays" like *thromboelastography* have proven to be more sensitive methods of monitoring hemostasis in trauma victims (see next).

Thromboelastography

Thromboelastography (TEG) provides information on clot initiation, progression, strength, and lysis from whole blood samples at body temperature. This is accomplished by placing a sample of blood in a cylindrical cup that has a central pin suspended in the sample. The cup is then rotated in an alternating clockwise and counterclockwise direction, and the stationary pin records the torque produced as the blood coagulates and then lyses. (An alternative method known as

rotational thromboelastometry or ROTEM, which uses a stationary cup and a rotating pin, is not described here.)

A typical TEG tracing, which is shown in Figure 15.5, is a record of the resistance to oscillations in the sample (used as a measure of clot firmness) over time. The symmetrical curves are produced by the alternating clockwise and counterclockwise rotation of the blood sample. The relevant measures are as follows (34):

. R is the "reaction time", or is the time to initiation of clot formation. The normal R time is 5–10 minutes, and is prolonged by defects in the coagulation cascade, including those produced by all anticoagulants except warfarin (i.e., the INR is the only reliable measure of warfarin anticoagulation).

. k is the "kinetic time", and is the time from clot initiation to a resistance of 20 mm. The normal k time is 1–3 minutes.

. The α angle represents the early rate of clot formation, and is dependent on fibrin polymerization. A normal α angle is 53–72°.

. MA is the maximum amplitude, and is a measure of clot strength. A normal amplitude is 50–70 mm, and is a reflection of fibrinogen cross-bridging of platelets.

. LY30 is the percentage of clot lysis that occurs from maximal amplitude (MA) to 30 minutes. This is a measure of fibrinolysis, and the normal range is 2.3–5.7%.

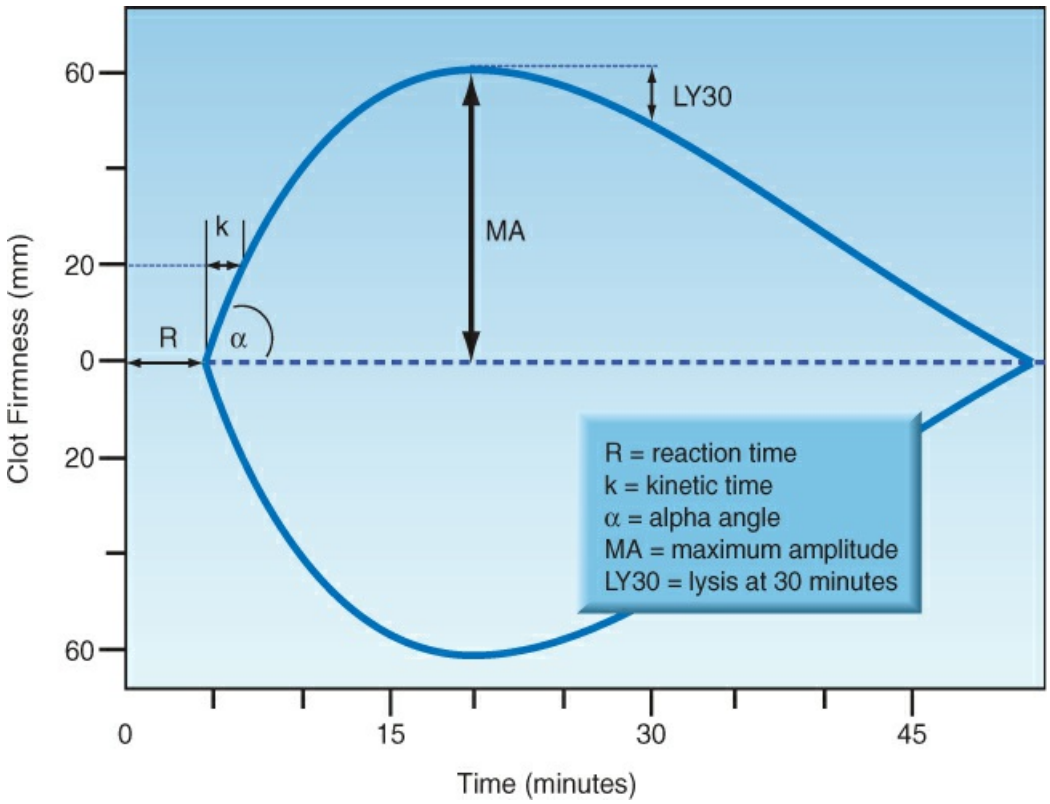

FIGURE 15.5 A thromboelastography tracing with identified components. See text for explanation.

TEG-Guided Therapy

The TEG measures just described can be used to guide hemostatic therapy as shown in Table 15.5. Clinical studies involving both trauma victims and postoperative patients with life-threatening hemorrhage (35,36) have shown that hemostatic management guided by TEG improves survival and reduces the use of blood products.

TABLE 15.5 Interventions Based on Thromboelastography

Measure	Abnormal Value	Intervention
Reaction (R) Time	>9 minutes	Transfuse plasma, or reverse anticoagulants (except warfarin)
Kinetic (k) Time	>2.5 minutes	Transfuse plasma
Alpha (α) Angle	<65°	Cryoprecipitate or fibrinogen concentrate
MA (max amplitude)	<55 mm	Transfuse platelets
LY30 (lysis in 30 min)	>3%	Tranexamic acid

From Reference 34.

Goals of Resuscitation

The overall goals of resuscitation for hemorrhagic shock are summarized in Figure 15.6. Many of the tissue perfusion and oxygenation goals have been presented elsewhere in the book, while the hemostasis goals have just been described. Unfortunately, achieving these goals does not ensure a satisfactory outcome, as described next.

POSTRESUSCITATION INJURY

An apparent successful resuscitation of hemorrhagic shock can be followed in 48–72 hours by progressive multiorgan failure (37). The earliest manifestation is progressive respiratory dysfunction, which is followed within days by progressive dysfunction of the kidneys, liver, heart, and central nervous system. The mortality rate is determined by the number of organs involved, and averages 50–60% (37).

Pathophysiology

Postresuscitation injury is a form of *reperfusion injury* (38) that is believed to originate in the splanchnic circulation, where reperfusion of ischemic bowel releases proinflammatory cytokines that gain access to the systemic circulation and incite a systemic inflammatory response that is responsible for the multiorgan damage.

Several factors predispose to postresuscitation injury, including the time required to reverse the shock, the volume of crystalloid resuscitation (which promotes bowel edema and predisposes to the abdominal compartment syndrome), and the number of units of RBCs transfused (>6 units in 12 hrs) (38). Infection of bowel origin may be involved if the onset of multiorgan failure is more than 3 days after the resuscitation (38).

Management

There is no specific therapy for postresuscitation injury, and preventive measures such as rapid reversal of the shock state, and limiting the infusion of crystalloid fluids and RBC products (if possible) may be helpful. In late-onset multiorgan failure (onset >72 hrs after resuscitation), recognition and prompt treatment of an underlying sepsis is essential.

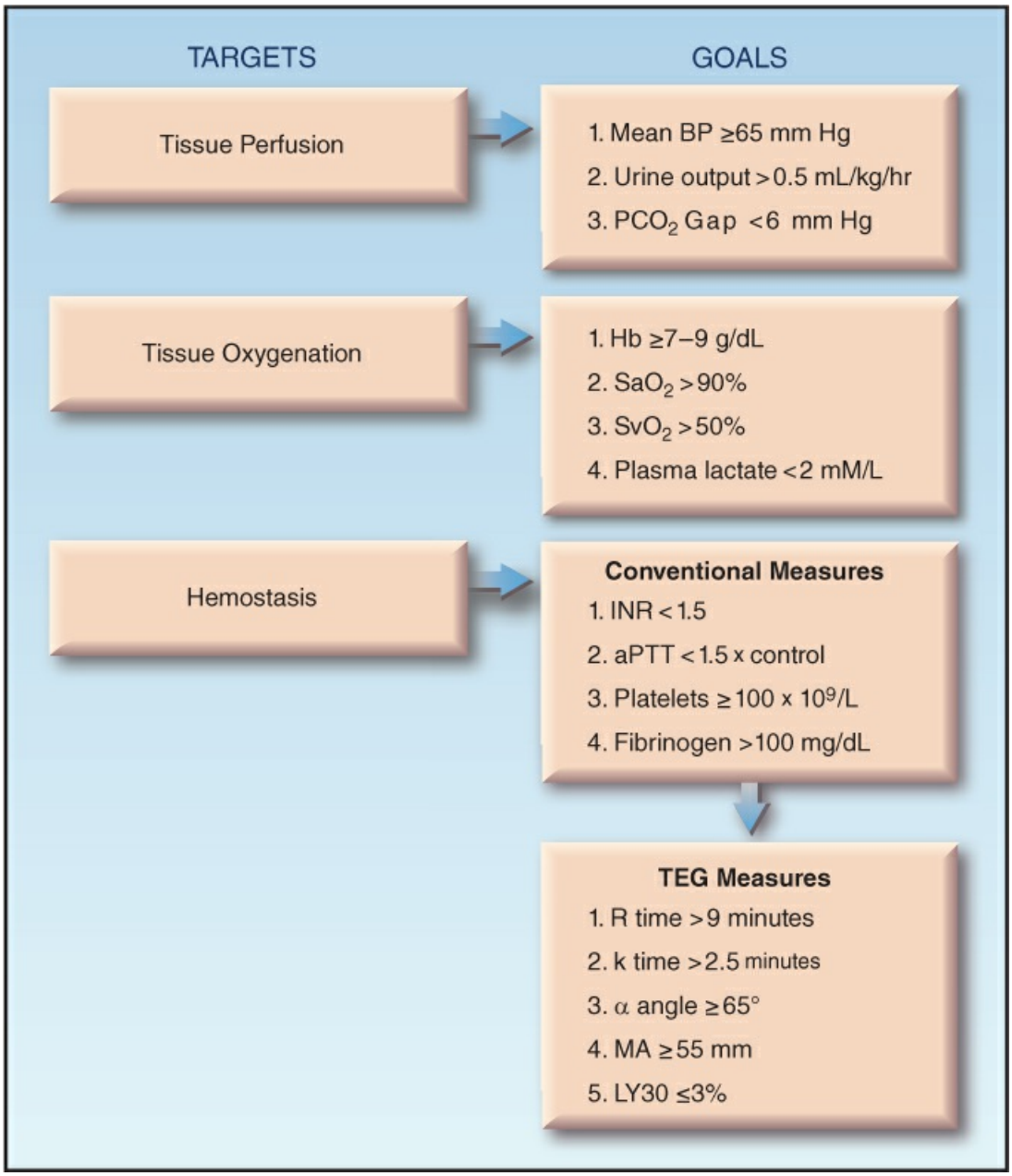

FIGURE 15.6 A summation of the goals of resuscitation in hemorrhagic shock.

A FINAL WORD

A Summation

The resuscitation of hemorrhagic shock should incorporate the following elements (in addition to timely source control):

. Use short, large-bore catheters, and avoid hypothermia by warming infusates to 37° C (e.g., with a rapid infusion system).

. Restrict the use of crystalloid fluids to 1 or 2 liters before using blood products (if possible).

. Replace blood components in a ratio that will mimic whole blood replacement, and consider the adjunctive measures shown in Figure 15.4.

. Consider "permissive hypotension" until the bleeding is controlled. The target BP in this approach is a systolic pressure of 80–90 mm Hg or a mean pressure of 50 mm Hg, which is maintained as long as there is evidence of adequate tissue perfusion (e.g., plasma lactate <2 mmol/L).

. If possible, use thromboelastography (or rotational thromboelastometry) to guide hemostatic management (see Figure 15.5 and Table 15.5).

And if the resuscitation is successful, remember to remain vigilant for the appearance of postresuscitation organ injury and sepsis of bowel origin.

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Chapter 16

Cardiogenic Shock

When is a piece of matter said to be alive? When it goes on "doing something," moving, exchanging material with its environment.

Erwin Schrödinger (*a*)

The human organism goes on exchanging material with its environment by virtue of a circulatory system equipped with an automatic stroke pump that averages about 100,000 stroke cycles daily, and pumps a daily volume of about 8,000 liters through a network of conducting vessels that, if placed end-to-end, would stretch more than 60,000 miles (more than twice the circumference of the Earth!) (1). Failure of this remarkable circulatory system begins and ends with cardiac pump failure, which can be categorized as "concerning" (conventional heart failure), "life-threatening" (cardiogenic shock), or "catastrophic" (cardiac arrest).

This chapter focuses on the challenging condition of cardiogenic shock, where management is designed to allow time for the heart to heal from a recent insult (e.g., acute myocardial infarction), or for a definitive procedure to be performed (e.g., bypass surgery). The real challenge in cardiogenic shock, however, is that half of the patients do not survive despite the best management efforts (2).

PATHOPHYSIOLOGY

Cardiogenic shock can be described as cardiac pump failure that results in inadequate O_2 delivery to tissues and impaired oxidative metabolism. The culmination of this condition is multiorgan failure and a fatal outcome.

Etiologies

Acute myocardial infarction is responsible for about two-thirds of the cases of cardiogenic shock (3), while the remaining cases can arise from a variety of cardiac disorders (see later).

Acute Myocardial Infarction

Cardiogenic shock develops in 5–10% of cases of acute myocardial infarction (3), and the mechanisms involved are shown in Figure 16.1. Infarction of the left ventricle is responsible for

about 80% of the cases, and requires loss of at least 40% of the functional mass of the ventricle (2). Infarction of the right ventricle is implicated in less than 5% of cases (3). There are also three infarct-related complications that can produce cardiogenic shock, as described below.

. Rupture of the papillary muscles (7% of cases) results in acute and life-threatening mitral insufficiency. (*Note:* The papillary muscles attach, via the chordae tendinae, to the leaflets of the mitral valve, and contraction of these muscles prevents prolapse of the mitral valve during ventricular systole.)

. Rupture of the interventricular septum (4% of cases), is accompanied by a large left-to-right shunt, which floods the pulmonary circulation and diverts flow away from the systemic circulation.

. Rupture of the ventricular wall (1% of cases) is a catastrophic complication of transmural infarctions, and results in a rapidly-accumulating hemopericardium and pericardial tamponade.

These complications typically appear within 24 hours of the infarction (2), which is contrary to the traditional notion that they are late-onset complications.

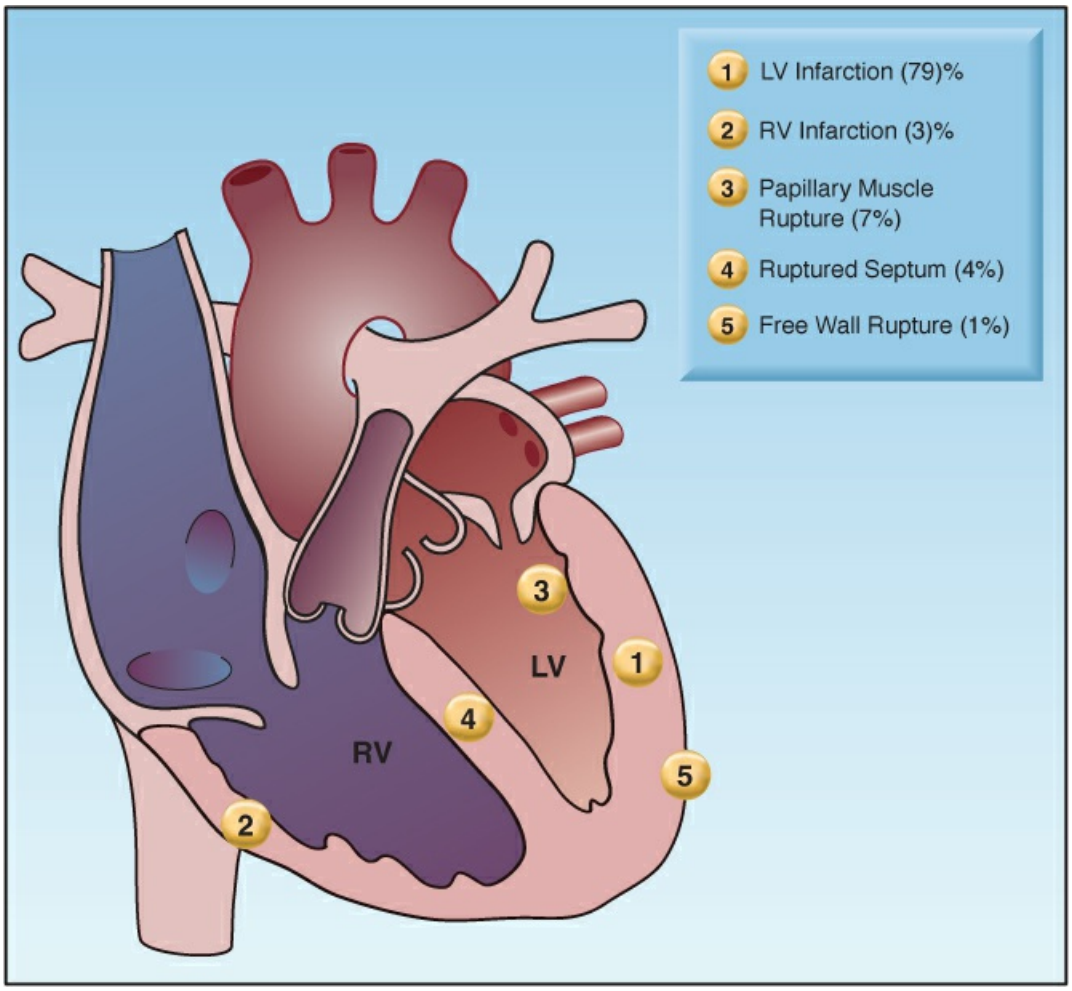

FIGURE 16.1 The mechanisms of cardiogenic shock from acute myocardial infarction. Percentages from Reference 3. **LV** = left ventricle, **RV** = right ventricle.

Other Conditions

The last decade has witnessed an increase in cases of cardiogenic shock that are unrelated to acute myocardial infarction (3), and the major ones are listed in Table 16.1. Acute exacerbations of chronic heart failure have been identified in as many as 30% of cases of cardiogenic shock (2), and stress-induced (Takotsubo's) cardiomyopathy has emerged as a potential culprit. Other notable conditions are summarized below.

DYNAMIC OUTFLOW OBSTRUCTION: In cases of hypertrophic cardiomyopathy, the flow of blood through the narrowed left ventricular outflow tract can create a suction effect that pulls the mitral valve leaflets anteriorly, and mid-systolic contact of the mitral valve and the interventricular septum creates a "dynamic left ventricular outflow obstruction"(4). The diagnosis of this condition is made with continuous wave Doppler ultrasound in the apical four-chamber view, which is used to calculate the peak systolic pressure gradient across the subaortic region of the left ventricle (5).

Recognition of this condition is important because it is treated differently than other causes of cardiogenic shock: i.e., the goal of management in this case is to slow the heart rate and increase diastolic filling, using nonvasodilating beta-blockers (e.g., metoprolol, nadolol).

CARDIAC SURGERY: Cardiogenic shock is reported in 2–5% of patients who undergo cardiac surgery (6), and this *postcardiotomy shock* can begin in the operating room or in the early postoperative period. Presumed mechanisms include myocardial hibernation or "stunning", and inadequate cardioprotection. Vasodilation may also play a role in the hypotension (6).

PREGNANCY: There is an idiopathic cardiomyopathy that can appear in the later stages of pregnancy or in the early months following delivery, and is characterized by systolic dysfunction and a variable clinical course. The incidence of this *peripartum cardiomyopathy* in the United States is 1 case per 3,000–4,000 pregnancies (7), and the risk factors include age >30 years, multigestational pregnancy, African heritage, and a family history of cardiomyopathy. This condition can progress to cardiogenic shock and even cardiac arrest, and it has a reported mortality rate of 7–20% in the United States (7).

Obstructive Shock

The category known as "obstructive shock" is essentially cardiogenic shock that is caused by conditions that are extrinsic to the heart. These conditions include acute pulmonary embolism, pericardial tamponade, and tension pneumothorax. The hemodynamic consequences are the same as those of cardiogenic shock, and the management is aimed at correcting the responsible condition.

TABLE 16.1 Causes of Cardiogenic Shock Other than Acute MI

General	Specific Circumstances
Chronic heart failure with acute decompensation	Postcardiotomy shock
Acute myocarditis	Peripartum cardiomyopathy
Takotsubo's cardiomyopathy	Post-cardiac arrest shock
Dynamic outflow obstruction	

Advanced valvular disease	

Hemodynamic Changes

The hemodynamic changes in cardiac pump failure are demonstrated in Figure 16.2. The decrease in cardiac output is accompanied by an increase in cardiac filling pressures (either the central venous pressure or the pulmonary artery wedge pressure, depending on which ventricle has failed), and an increase in systemic vascular resistance (due to activation of both the sympathetic nervous system and the renin-angiotensin-aldosterone system). These changes occur in both heart failure and cardiogenic shock, and *cardiogenic shock is distinguished from heart failure by the presence of tissue hypoperfusion (e.g., hypotension, decreased urine output) and inadequate tissue oxygenation (e.g., elevated plasma lactate levels).*

Right Heart Failure

Cardiogenic shock from right ventricular (RV) failure has many similarities to shock from left ventricular (LV) failure, but it has a lower mortality rate (8). Some of the features that identify RV failure include an increase in the CVP/PAWP ratio, a dilated RV, and a normal LV ejection fraction. Severe RV dilation can push the interventricular septum into the chamber of the left ventricle, which reduces LV filling and further impairs cardiac stroke output. (The diagnosis and management of RV failure is presented in Chapter 18.)

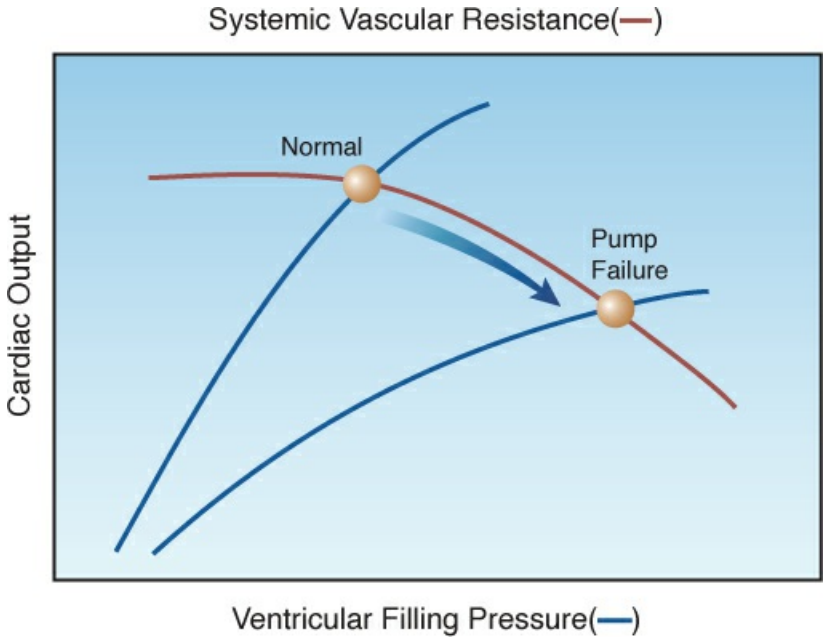

FIGURE 16.2 Graph showing the hemodynamic changes in cardiac pump failure.

Exceptions

The cardiac index (CI) in cardiogenic shock is typically <2.2 L/min/m^2 (normal CI = 2.4–4.0 L/min/m^2) (9), but the cardiac filling pressures are not increased in as many as 30% of patients with infarct-related cardiogenic shock (2). In addition, the systemic vascular resistance may not be elevated when cardiogenic shock is accompanied by systemic inflammation (see later). Finally, hypotension is absent in about 5% of cases of cardiogenic shock (2).

The Microcirculation

Studies using sublingual videomicroscopy have shown that cardiogenic shock is associated with a decrease in capillary perfusion that is independent of the changes in global hemodynamic measures (i.e., cardiac output and blood pressure), and it has a greater impact on mortality than the "macrocirculatory" changes (10). This *microcirculatory dysfunction might explain why correcting the cardiac output and blood pressure in cardiogenic shock does not ensure survival* (10,11). Monitoring microcirculatory perfusion with the PCO_2 gap is potentially useful in this regard (see later).

Systemic Inflammation

Myocardial necrosis triggers a localized inflammatory response (12), which can progress to a systemic inflammatory response. Signs of systemic inflammation (e.g., fever, leukocytosis, etc.) have been reported in 20–40% of patients with cardiogenic shock complicating acute myocardial infarction, and these patients have a lower SVR (due to the vasodilating effects of nitric oxide) and a higher mortality rate (13). This *systemic inflammation has been linked to the microcirculatory dysfunction in cardiogenic shock* (13).

MANAGEMENT

Since most cases of cardiogenic shock are associated with acute myocardial infarction, the management of cardiogenic shock often includes measures aimed at coronary revascularization (i.e., coronary angioplasty, bypass surgery, antithrombotic therapy). These measures are described in Chapter 20; the focus here is on measures that promote tissue perfusion.

Monitoring

The management of cardiogenic shock requires a reliable measure of the cardiac output, and the most reliable measurement available is the thermodilution cardiac output provided by pulmonary artery (PA) catheters (see Chapter 8). These catheters also provide measurements of the cardiac filling pressures (the central venous and wedge pressures), the systemic vascular resistance, and the oxygen transport variables (see Table 8.1), which makes them ideal for the management of cardiogenic shock. In fact, the use of PA catheters has been shown to improve outcomes in cardiogenic shock (14), and the most recent guidelines from the American Heart Association emphasizes the value of PA catheters in the management of cardiogenic shock (15).

Tissue Perfusion & Oxygenation

As mentioned earlier, cardiogenic shock can be accompanied by deficits in microcirculatory flow that are independent of the changes in cardiac output, and can persist after the cardiac output and blood pressure are normalized. This highlights the value of monitoring tissue perfusion with the PCO_2 gap (described in Chapter 14), and with clinical signs of organ perfusion (e.g., urine output).

Tissue oxygenation is probably the most important parameter to monitor in cardiogenic shock, since shock is defined as an abnormality in cellular oxygen utilization (see Chapter 14). Although it is not possible to directly monitor tissue O_2 levels, the mixed venous O_2 saturation

(SvO_2) can provide information about the balance between O_2 delivery and O_2 consumption, and plasma lactate levels provide an indirect assessment of the adequacy of tissue oxygenation. (These measures are described in Chapter 9.)

Goals of Management

The goals of hemodynamic management in cardiogenic shock are summarized in Table 16.2. Some of these goals are based on the normal range of values for the variable, and some are based on the lowest or highest tolerable levels. An example of the latter instance is presented next.

Optimizing Filling Pressures

As mentioned earlier, the left ventricular filling pressure (i.e., the pulmonary artery wedge pressure) is not always elevated in cardiogenic shock (2), and when this occurs, volume infusion can be instrumental in augmenting the cardiac output. The target of volume infusion is the highest filling (wedge) pressure that will augment cardiac output without producing pulmonary edema, and this "optimal" pressure is dependent on the colloid osmotic pressure (COP) of plasma. The plasma COP is normally about 28 mm Hg (16), but a lower COP of 20–25 mm Hg seems more reasonable in critically ill patients, who often have a subnormal plasma albumin concentration (the major determinant of plasma COP). Thus, *the optimal left ventricular filling pressure (i.e., wedge pressure) is considered to be 18–20 mm Hg* (17).

TABLE 16.2 Goals of Management in Cardiogenic Shock

Category	Goals
Hemodynamics	PAWP = 19–20 mm Hg CI ≥2.5 L/min/m^2 SVRI = 25–30 Wood Units[§] Mean BP ≥65 mm Hg
Tissue Perfusion	PCO_2 Gap <6 mm Hg Urine output >0.5 mL/kg/h
Tissue Oxygenation	SvO_2 >50% Plasma lactate <2 mmol/L

[§]Wood Units = mm Hg/L/min/m^2.

Vasopressor Therapy

Hypotension is almost universal in cardiogenic shock, and vasoconstrictor agents (vasopressors) are used to raise the blood pressure to a systolic BP ≥90 mm Hg or a mean BP ≥65 mm Hg. The vasopressors available for clinical use are described in Chapter 14. *The vasopressor of choice in cardiogenic shock is norepinephrine* (15,18,19), a catecholamine that produces systemic vasoconstriction and mild cardiac stimulation. One exception to the norepinephrine preference is cardiogenic shock from dynamic LV outflow obstruction, where a pure vasoconstrictor like phenylephrine (which can trigger a reflex bradycardia) is more appropriate (15).

Norepinephrine

The preference for norepinephrine in cardiogenic shock comes from studies comparing norepinephrine with other popular vasopressors (epinephrine and dopamine), which showed that norepinephrine had a lower risk of tachycardia and troublesome arrhythmias, and was associated with fewer deaths (18,20,21). The mild cardiac stimulation produced by norepinephrine tends to preserve cardiac output in the face of vasoconstriction, at least in the lower dose range.

DOSING: Norepinephrine is given by continuous infusion (without a loading dose) starting at a rate of 5 µg/min (or 0.05 µg/kg/min), and titrating upward every 5 minutes to achieve the desired blood pressure. The usual dose rate in studies of cardiogenic shock is 5–30 µg/min (or 0.05–0.5 µg/kg/min) (20).

Inotropic Therapy

Vasopressor therapy does not alleviate the cardiac pump failure, and can aggravate it. As a result, drugs that increase cardiac contractile force (inotropic agents) are typically added to vasopressor therapy. There are only a few inotropic agents used in this setting, and these are included in Table 16.3, along with their dosing regimens. Inotropic therapy is contraindicated in cardiogenic shock from dynamic LV outflow obstruction.

Dobutamine

The most widely used inotropic agent in cardiogenic shock is dobutamine (18,22), a synthetic catecholamine that stimulates β_1 receptors in the heart, and increases both cardiac stroke output and heart rate. Dobutamine also has mild vasodilator effects, but it does not decrease the blood pressure because the vasodilator effect is offset by the increase in cardiac stroke output. This ability to preserve (and sometimes augment) the blood pressure is the principal advantage of dobutamine over other inotropic agents in cardiogenic shock.

The major disadvantages of dobutamine include an increase in heart rate (which is usually 5–15 beats/min, but can exceed 30 beats/min), and an increase in myocardial O_2 consumption (23). These changes are associated with an increase in cardiac work, which is deleterious in the setting of acute myocardial infarction, and also in the failing myocardium (where cardiac work is already increased).

TABLE 16.3 Inotropic Agents for Cardiogenic Shock

Agent	Dosing Regimen and Comments	
Dobutamine	1. Start infusion at 3–5 µg/kg/min, and increase in increments of 3–5 µg/kg/min, if needed. Usual dose is 3–20 µg/kg/min. 2. Major disadvantage is an increase in heart rate.	
Milrinone	1. Initial dose is 50 µg/kg (over 10 min), followed by an infusion rate of 0.375–0.75 µg/kg/min. Daily dose should not exceed 1.13 mg/kg. 2. Dose adjustments are advised for renal insufficiency:§	
	Creatinine Clearance	**Infusion Rate**
	50 mL/min/1.73 m^2 40	0.43 µg/kg/min 0.38

	30 20	0.33 0.28
	3. Major disadvantage is the risk of hypotension.	
Levosimendan	1. Initial dose is 12 µg/kg (over 10 min), followed by an infusion rate of 0.1 µg/kg/min. After 1 hour, infusion rate can be increased to 0.2 µg/kg/min, if needed. 2. Has a long half-life (80 hrs). 3. Approved for use in about 60 countries, but not in the United States.	

§Dosing adjustments are manufacturers recommendation (24).

Milrinone

Milrinone is a phosphodiesterase inhibitor that acts as an inotrope by virtue of inhibiting the breakdown of cyclic AMP, which enhances cyclic AMP-mediated calcium influx into cardiac myocytes. It also acts as a vasodilator, which further promotes cardiac stroke output. However, the vasodilator actions of milrinone can produce troublesome hypotension (23), which is a major drawback in cardiogenic shock. The elimination half-life of milrinone (2.5 hrs) is significantly prolonged in patients with renal insufficiency, and a dosing adjustment is recommended when the creatinine clearance is <50 mL/min/1.73 m^2 (24), as shown in Table 16.3.

The inotropic effects of milrinone are comparable to those of dobutamine, but there is less risk of troublesome tachycardia (23). Despite this lower risk of tachycardia, milrinone has a significant risk of hypotension, and this limits its popularity as an inotrope in cardiogenic shock. Milrinone is more appropriate for the management of decompensated heart failure without hypotension.

Levosimendan

Levosimendan increases cardiac contractility by sensitizing cardiac myofilaments to calcium, and also promotes vasodilation by facilitating potassium influx into vascular smooth muscle (25). This drug is particularly appealing in infarct-related cardiogenic shock because it dilates coronary arteries and does not stimulate myocardial O_2 consumption. This might explain why studies comparing dobutamine and levosimendan show a mortality benefit with levosimendan (26). However, there is a risk of hypotension with levosimendan, which is a disadvantage. Levosimenden has a long half-life (80 hrs), and infusions are usually limited to 24 hours.

Levosimendan has been a popular inotrope in Europe and South America since it was introduced in 2000 (25), but it is not approved for use in the United States.

Cardiac Workload

The pharmacological management of cardiogenic shock has the unfortunate consequence of increasing the workload of the heart (e.g., vasopressors will increase left ventricular afterload, and inotropes will increase contractility, and can increase heart rate). The increase in cardiac work is counterproductive in the failing myocardium, and seems unlikely to facilitate any improvements in “native” cardiac function. On the other hand, mechanical support devices (described next) are designed to reduce cardiac work, and thus it is important to *avoid delays in proceeding to mechanical cardiac support if there is no evidence of rapid improvement during pharmacological support* (15).

MECHANICAL CARDIAC SUPPORT

Mechanical cardiac support (MCS) is generally reserved for cases of refractory cardiogenic shock where improvement in cardiac function is an expectation (usually after myocardial infarction or cardiac surgery), or another intervention is planned (e.g., coronary bypass surgery) (27).

Intra-Aortic Balloon Pump

The intra-aortic balloon pump (IABP) is the oldest form of MCS (introduced in the 1960s), and continues to be used despite evidence that it does not improve survival (28). However, *studies comparing the IABP with other forms of MCS have shown no improvement in survival with any of the methods* (15). (This seems to be a testament to the whole MCS approach to cardiogenic shock, however there are individual patients who benefit from MCS, and it is often difficult to predict who will benefit prior to the intervention.) The IABP is the most readily available form of MCS in hospitals other than large, tertiary medical centers, but it is only a temporary measure. It is contraindicated in patients with aortic valve insufficiency or aortic dissection.

The Method

The intra-aortic balloon is an elongated polyurethane balloon that is inserted percutaneously into the femoral artery and advanced up the aorta until the tip lies just below the origin of the left subclavian artery (see Figure 16.3). A pump attached to the balloon uses helium, a low density gas, to rapidly inflate and deflate the balloon (inflation volume is generally 35 to 40 mL). Inflation begins at the onset of diastole, just after the aortic valve closes (the R wave on the ECG is a common trigger). The balloon is then deflated at the onset of ventricular systole, just before the aortic valve opens (during isovolumic contraction). This pattern of balloon inflation and deflation produces two changes in the aortic pressure waveform, which are illustrated in Figure 16.3.

. Inflation of the balloon during diastole increases the peak diastolic pressure, which augments coronary blood flow (which occurs predominantly during diastole), and also increases the mean arterial pressure (equivalent to the integrated pressure under the aortic pressure waveform), which augments systemic blood flow.

. Deflation of the balloon creates a suction effect that reduces pressure in the aorta when the aortic valve opens, and this decreases left ventricular afterload and augments ventricular stroke output.

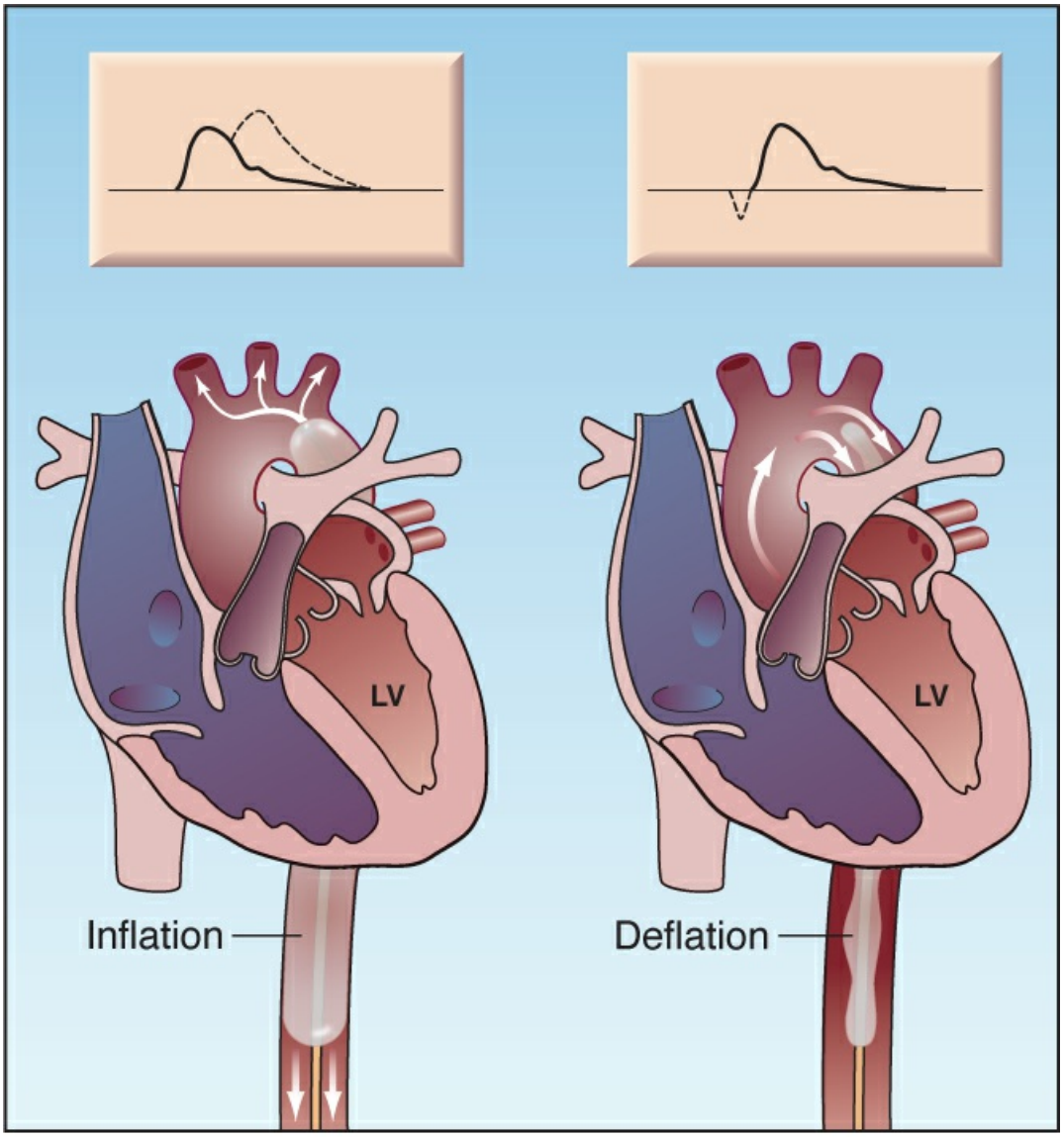

FIGURE 16.3 Intra-aortic balloon counterpulsation, showing balloon inflation in early diastole (on the left), and balloon deflation in late diastole (on the right). The associated changes in the aortic pressure (indicated by the dotted lines) are shown above each maneuver. The arrows show the direction of enhanced flow.

The IABP thus reduces cardiac work by unloading the left ventricle while also increasing coronary blood flow and systemic flow.

Complications

The principal concern with IABP is limb ischemia, which can appear while the balloon is in place or shortly after balloon removal., Most cases are the result of in-situ thrombosis at the catheter insertion site, but aortoiliac injury may also be responsible. Loss of distal pulses alone does not warrant removal of the balloon as long as sensorimotor function in the legs is intact (29). Loss of sensorimotor function in the legs should always prompt immediate removal of the device, and surgical intervention may be required.

Other complications of IABP include septicemia, balloon rupture, peripheral neuropathy, and pseudoaneurysm. Fever is reported in 50% of patients during IABP support, but bacteremia is reported in only 15% of patients (30).

Impella Catheters

Impella® catheters (ABIOMED, Inc., Danvers, MA) provide flow assistance for ventricular output. These catheters are primarily used as left-ventricular assist devices (LVADs), but there is also a catheter designed to assist the right ventricle (an RVAD).

An example of an Impella catheter shown in Figure 16.4. The catheter is equipped with a miniature centrifugal pump (i.e., the type of pump that uses rotational "propeller" blades to create non-pulsatile flow), and it is inserted percutaneously into a femoral artery and advanced into the left ventricle. (The pigtail at the tip of the catheter allows the catheter to be advanced safely.) The pump moves blood from the left ventricle to the proximal aorta at flow rates of 2.5–5.5 L/min (flow rates differ with different catheters). The device shown in Figure 16.4 monitors the native cardiac output, and automatically adjusts the pump flow to achieve a (pre-selected) total cardiac output (31).

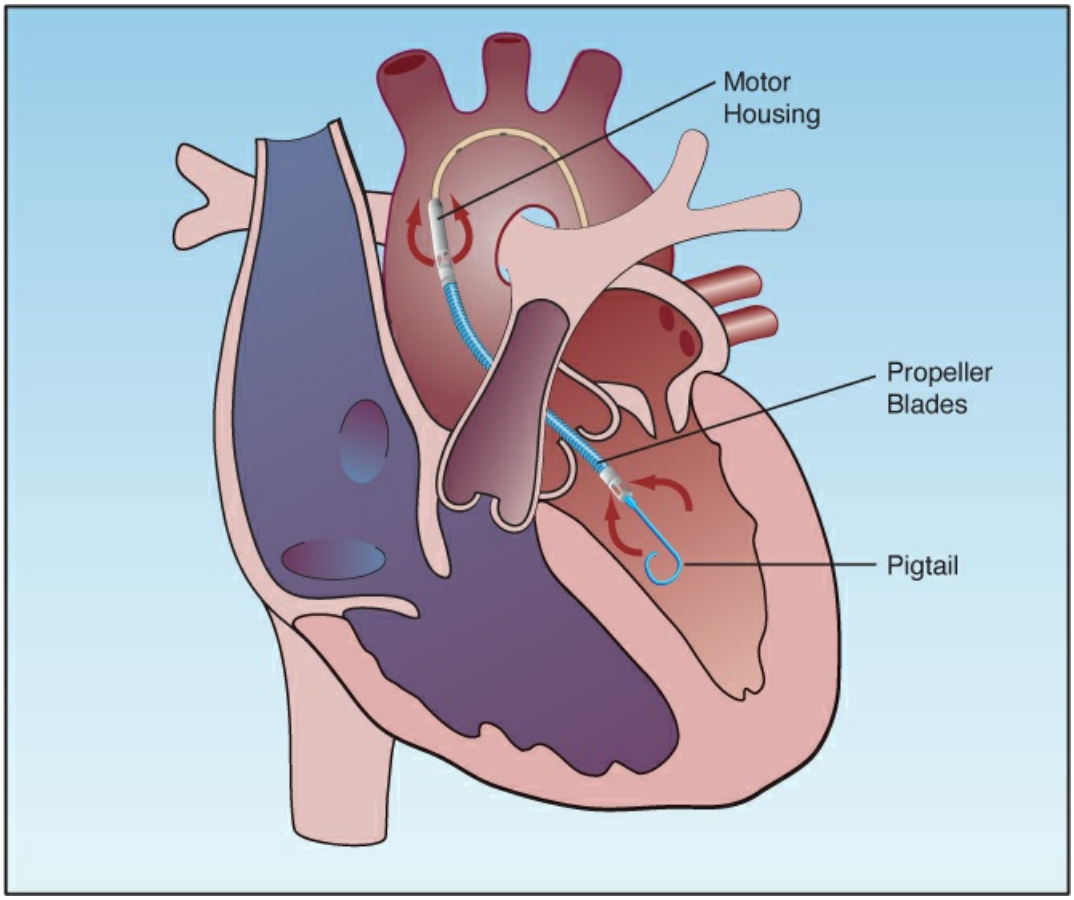

FIGURE 16.4 An Impella catheter, which is equipped with a miniature centrifugal pump. The tip of the catheter is placed in the left ventricle so that the pump's rotational propellers are positioned across the aortic valve. The pump then transfers blood from the ventricle to the proximal aorta (see directional arrows) to unload the ventricle. See text for further explanation.

The hemodynamic effects of Impella catheters are similar to the IABP; i.e., they unload the left ventricle and increase cardiac output, while also increasing coronary blood flow (32). This similarity also extends to survival value, since Impella catheters have not shown a survival advantage over IABP in patients with infarct-related cardiogenic shock (28,33). Impella catheters have more of an advantage in patients with end-stage left ventricular failure, since they can be implanted for long-term use. These catheters are contraindicated in patients with aortic valve disease or a prosthetic aortic valve, and in patients with an LV thrombus.

Complications

The complications of the Impella catheter are similar in type to the IABP, but there is evidence that major bleeding and limb ischemia are more common with Impella catheters (33,34). The incidence of significant hemolysis (5–10%) is also greater with Impella catheters than with other forms of mechanical support (35).

ECMO

Extracorporeal membrane oxygenation (ECMO) is designed to support both circulatory flow and pulmonary gas exchange. Veno-arterial ECMO (VA-ECMO) is used for cardiogenic shock, and is gaining in popularity for the management of refractory cardiogenic shock associated with acute myocardial infarction and cardiac surgery. VA-ECMO offers some advantages, including the ability to provide full biventricular support (matched only by combining RV and LV Impella catheters), and the ability to support oxygenation and CO_2 removal, which is advantageous in patients with respiratory failure (a common complication of cardiogenic shock). *VA-ECMO is the preferred method of mechanical support in cases of cardiogenic shock associated with respiratory failure* (36).

The basic elements of a VA-ECMO circuit are shown in Figure 16.5. Vascular access can be achieved by percutaneous cannulation of the femoral artery and vein. The femoral vein catheter is advanced along the inferior vena cava until the tip is situated close to the right atrium. Blood from the femoral vein catheter is passed through a centrifugal pump (which generates the desired pressures and flow rates) and then flows through a membrane oxygenator before being warmed to 37° C and returned via the femoral artery catheter. Retrograde flow up the aorta is intended to reach the aortic arch so it can enhance cerebral blood flow. Flow rates vary according to each patients native cardiac output, but they can reach 5–6 L/min to provide full circulatory support. As in the other forms of mechanical support, full anticoagulation is necessary.

Complications

The complications of VA-ECMO are varied and considerable. Reported complications and their frequency of appearance are as follows (36): major bleeding (41%), sepsis (30%), limb ischemia (17%), lower extremity compartment syndrome (10%), stroke (6%), and lower limb amputation (5%).

LV AFTERLOAD: VA-ECMO has one problem that is not shared by the other forms of mechanical support: i.e., the retrograde flow in the aorta increases left ventricular (LV) afterload, and this can be severe enough to reduce LV output and cause acute pulmonary edema (36). Efforts to tackle this problem have included combining IABP or Impella catheters with VA-ECMO to

reduce LV afterload, and draining blood from the left ventricle to reduce end-diastolic pressure (known as “venting”) (37).

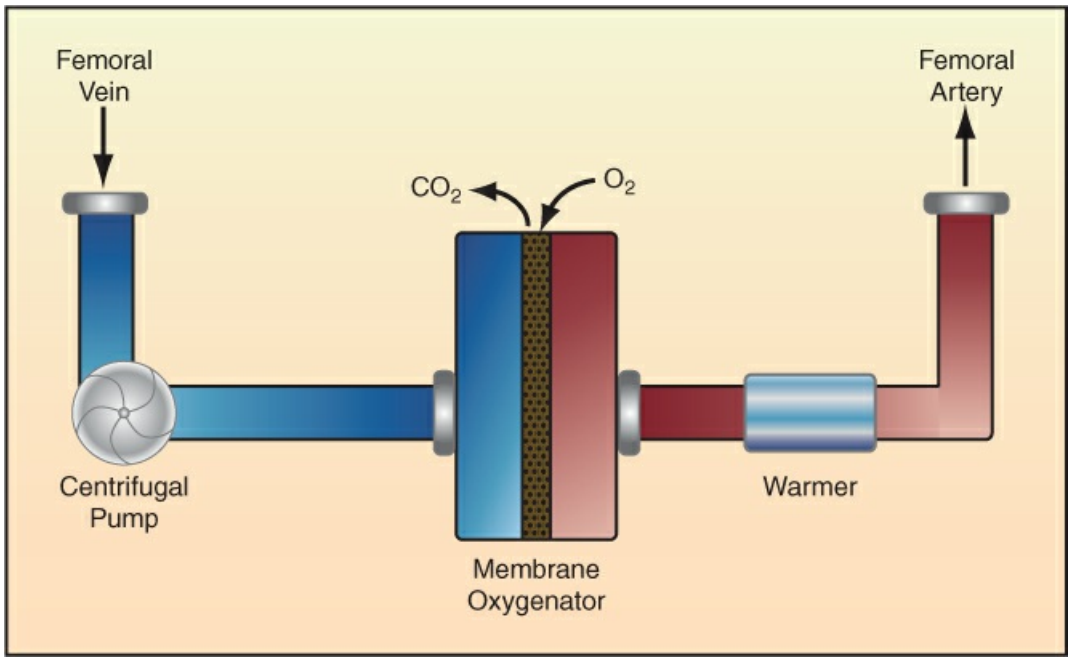

FIGURE 16.5 Schematic design of a VA-ECMO circuit. See text for explanation.

Outcomes

The largest registry of ECMO patients has reported a 42% survival rate to hospital discharge when VA-ECMO is used for cardiogenic shock (38). A comparison of survival rates with VA-ECMO versus other forms of mechanical support (IABP or LVAD) has had inconsistent results; i.e., survival rates have been better with VA-ECMO in some reports (39) and better with the Impella catheter in other reports (40).

Device Selection

The choice of mechanical support device will largely be determined by availability and individual preferences at your hospital. VA-ECMO is the method of choice for cardiogenic shock associated with respiratory failure, and there is a trend in favor of VA-ECMO for all mechanical support. However, ECMO is not available in many hospitals, and mechanical support with IABP or an LVAD may be the only options (patients can then be transferred for ECMO if there is no improvement). Impella catheters are preferred to IABP in many hospitals, even though the outcomes appear to be the same with both devices.

A FINAL WORD

The following information in this chapter deserves emphasis.

. The management of cardiogenic shock is aimed at “buying time” until either the heart begins to heal from an acute insult (e.g., an acute coronary event), or another intervention is

performed (e.g., bypass surgery).

. Pharmacological support is an immediate need for maintaining tissue perfusion, but this approach increases the workload of the heart, and is counterproductive. For this reason, proceeding to mechanical cardiac support should be a priority if there is no evidence of improvement with pharmacological support.

. Mechanical support devices can “unload” the ventricle (intra-aortic balloon pump), provide flow assistance for ventricular output (Impella catheters), or provide support for gas exchange and circulatory blood flow (VA-ECMO).

. VA-ECMO is the support method of choice if cardiogenic shock is accompanied by respiratory failure. Otherwise, there is no consistent evidence showing that one method is superior to the others for a satisfactory outcome.

. Avoiding delays to initiation of mechanical support will optimize outcomes. Mechanical support that is initiated after the onset of multiorgan failure has been described as a “bridge to nowhere” (36).

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Chapter 17

Inflammatory Shock Syndromes

Inflammation is not itself considered a disease but a salutary operation… but when it cannot accomplish that salutary purpose… it does mischief.

John Hunter, MD (*a*)

The introductory quote is from an 18th-Century British surgeon with an insatiable curiosity, who was known for his frequent grave-robbing soirees (for research material), and for a reckless self-experiment in which he inoculated himself with the purulent discharge from a patient with venereal disease, and subsequently developed both gonorrhea and syphilis (1). On a more positive note, John Hunter wrote the first definitive work on inflammation, where he noted that inflammation has two opposing "faces" (like a Janus face): i.e. it normally acts to promote healing from tissue injury or infection, but it can also become a *source* of tissue injury (2). Fast-forward over two hundred years, and the destructive face of inflammation has emerged as a major factor in a multitude of diseases, from acute (e.g., asthma) to chronic (e.g., atherosclerosis) to age-related (e.g., Alzheimer's) conditions.

This chapter describes three life-threatening conditions where inflammation plays a major role; i.e., septic shock, toxic shock, and anaphylactic shock. These conditions are examples of what happens when inflammation "does mischief".

INFLAMMATORY INJURY

The inflammatory response is a complex affair that is designed to eliminate external threats (e.g., from invading microbes) and to "cleanse" and heal damaged tissues. This operation is not typically harmful to the host, however severe or persistent inflammation can produce widespread tissue injury. Inflammatory tissue injury is especially problematic because it can become self-sustaining; i.e., the inflammatory injury can trigger another inflammatory response, which will produce more tissue injury, and so on. This condition of progressive inflammatory injury is known as *malignant inflammation*, and it plays a major role in the multiorgan failure that can complicate septic shock (see later) (3,4).

Neutrophil Activation

In the initial stage of the inflammatory response, circulating neutrophils experience a precipitous rise in cellular O_2 consumption (up to 20-fold) that lasts for 15–20 minutes (5). This is known as the *respiratory burst*, which is a misnomer, because the surge in O_2 consumption is not dedicated to the production of high-energy ATP molecules (i.e., cell respiration). Instead, the respiratory burst generates noxious chemical derivatives of oxygen that are used to kill invading microbes (5).

The reactions involved in the respiratory burst are shown in Figure 17.1. The trigger for this reaction sequence is activation of a specialized enzyme (NADPH oxidase) on the cell membrane, which initiates a series of reactions that adds electrons (one at a time) to oxygen. This generates a series of highly-reactive intermediates that include the *superoxide radical*, *hydrogen peroxide and the hydroxyl radical*. (A radical is an atom or molecule with an unpaired electron.) Neutrophils also have a myeloperoxidase enzyme that converts hydrogen peroxide to *hypochlorite*, a powerful germicidal agent that is the active ingredient in household bleach. These *reactive oxygen species* (ROS) are stored in cytoplasmic granules, and are released during neutrophil degranulation.

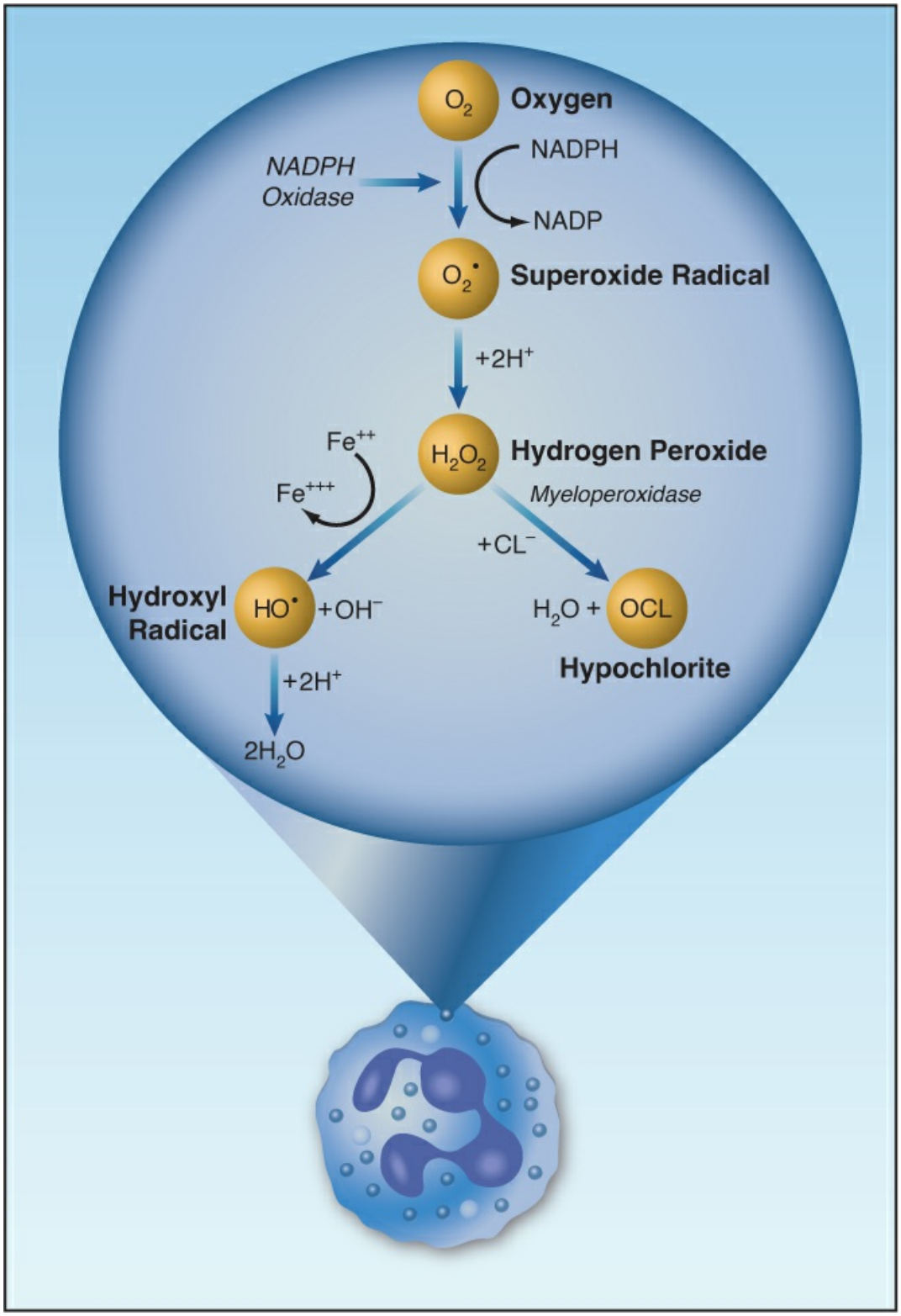

FIGURE 17.1 The sequence of reactions involved in the activation of neutrophils, which generates a series of reactive oxygen species (ROS) that are used to kill invading microbes. Free radicals are indicated by a superscripted dot. See text for further explanation.

The ROS are powerful oxidizing agents that are lethal for invading microbes. The role of

ROS in eradicating infectious organisms is demonstrated by a condition known as *chronic granulomatous disease*. This is a rare genetic disorder (with an incidence of 1:200,000 births in U.S.) in which the NADPH oxidase enzyme in neutrophils is defective, and patients with this disorder suffer from recurrent and life-threatening bacterial and fungal infections (6).

Oxidant Injury

ROS are also capable of damaging the tissues of the host, including the extracellular matrix, parenchymal cells, and the endothelium and its protective glycocalyx (7–9). The oxidizing effects of ROS can damage all vital cell components, including membrane lipids, all types of cellular proteins, and DNA molecules. This *oxidant injury* occurs when ROS activity exceeds the protective actions of endogenous antioxidants; a condition known as *oxidant stress*.
(*Note:* The destructive actions of oxygen on organic matter is evident when you consider why food is stored in vacuum-sealed containers, and why you wrap your sandwiches in cellophane.)

Inflammatory tissues are flooded with ROS, and the superoxide radical has been implicated as the source of inflammatory pain (10). Oxidant tissue injury usually begins to appear when the inflammation is persistent or progressive (possibly due to depletion of protective antioxidants). Furthermore, hydrogen peroxide moves freely through tissues, and can enter the bloodstream and reach distant organs, where it can enter cells and generate hydroxyl radicals when it encounters iron in the reduced state (Fe^{2+}) (see Figure 17.1). This is one possible mechanism for the multiorgan failure that can develop in patients with inflammatory lung injury (see Chapter 24), or sepsis (see later), as well as the postresuscitation syndrome after a cardiac arrest (see Chapter 21), which is a type of disseminated reperfusion injury.

Endothelial Dysfunction

Like neutrophils, endothelial cells are equipped with a NADPH oxidase enzyme that is activated in the early stages of the inflammatory response, and the resulting production of ROS is instrumental in promoting leukocyte adhesion to the endothelium and the migration of leukocytes into the tissues (11). However, inflammation also promotes endothelial dysfunction from oxidant stress (12), and this leads to increased capillary permeability and edema formation.

Oxidant stress at the endothelial level also reduces nitric oxide levels via the following reaction (13):

$$O_2\cdot + NO\cdot \rightarrow ONOO^- \qquad (17.1)$$

where $O_2\cdot$ is the superoxide radical, $NO\cdot$ is nitric oxide, and $ONOO^-$ is peroxynitrite. This reaction not only eliminates the beneficial actions of nitric oxide in promoting circulatory blood flow, it also generates a potent oxidative toxin (peroxynitrite) capable of extensive tissue injury (13).

Inflammatory Organ Injury

Inflammation can damage any of the vital organs, but the organs most often affected are listed in Table 17.1. These conditions pertain only to the inflammatory injury that occurs in critically ill patients, and they do not include the multitude of diseases caused by chronic inflammatory injury (e.g., rheumatoid arthritis, chronic obstructive lung disease). The most notable example of

inflammatory organ injury in critically ill patients is the acute respiratory distress syndrome (ARDS), which is a leading cause of acute respiratory failure that requires mechanical ventilation. (ARDS is the focus of Chapter 24.)

TABLE 17.1 Inflammatory Organ Injury in Critically Ill Patients

Organ System	Clinical Condition
Brain	Septic encephalopathy
Bone Marrow	Anemia of critical Illness
Circulatory System	Septic shock, Anaphylactic shock
Kidneys	Acute Kidney Injury
Lungs	Acute respiratory distress syndrome
Peripheral Nerves	Critical illness polyneuropathy
Skeletal Muscle	Critical illness myopathy, Rhabdomyolysis

The morbidity and mortality associated with inflammatory organ injury is not only related to the severity of involvement in individual organs, but also to the number of organs involved. This latter relationship is shown in Figure 17.2, which includes surveys from the United States (14) and Europe (15) showing a direct relationship between the mortality rate and the number of organ failures related to inflammation.

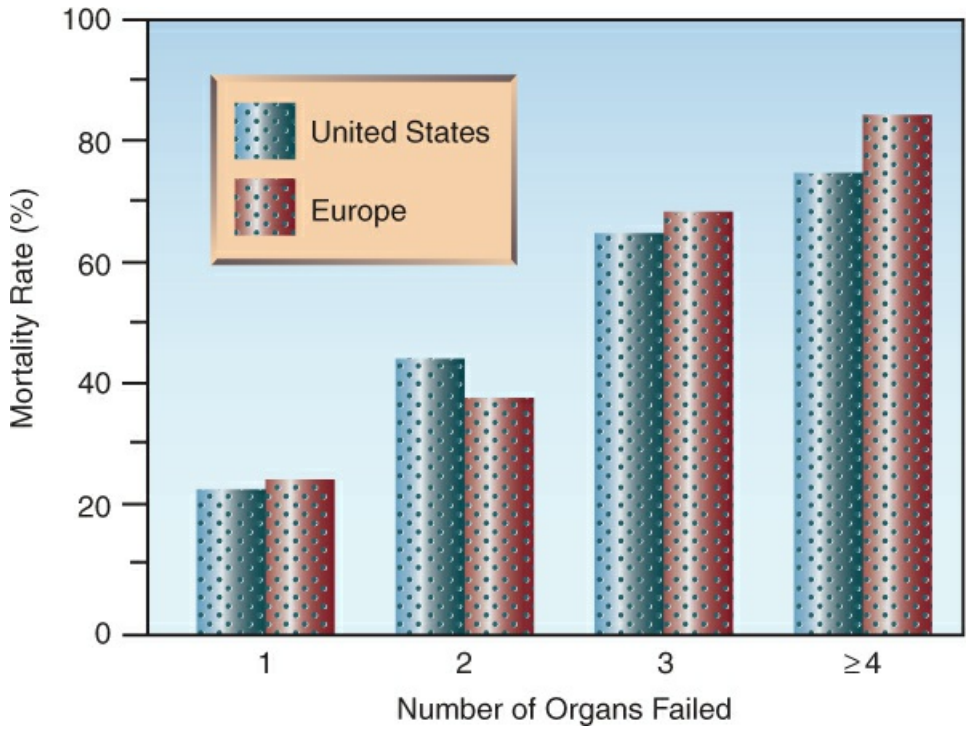

FIGURE 17.2 The relationship between mortality rate and the number of inflammation-related organ failures. Data from References 12 and 13.

SEPTIC SHOCK

Sepsis is responsible for one of every 2 to 3 in-hospital deaths in the United States (16), and one of every 5 deaths worldwide (17). The mortality rate varies by age and geographic locale: for septic shock in the United State, the mortality rate is about 30% when it is present on admission, and about 50% when it develops after admission (18). Despite the presumption of sepsis as infection, *the mortality rate in sepsis is not related to the causative organism, including multidrug-resistant organisms* (19). This observation is consistent with the notion that the major problem in sepsis is not the infection, but the host response to infection (see next).

Definitions

The current definitions of sepsis and septic shock are summarized below (20).

. Sepsis is an infection (suspected or confirmed) that is associated with life-threatening organ dysfunction, and is the result of a dysregulated host response to infection.

. Septic shock is a subset of sepsis that is characterized by the need for vasopressor support, and by a plasma lactate >2 mmol/L.

These definitions were introduced in 2016, and they replaced the prior definitions established in 1992 (21), which defined sepsis as an infection that was accompanied by a systemic inflammatory response (i.e., fever, leukocytosis, etc.) (21), with the latter condition being elevated to a syndrome; i.e., the "systemic inflammatory response syndrome", or SIRS. However, SIRS is a nonspecific finding in critically ill patients, as fewer than 50% of patients with SIRS have a documented infection (22,23), so SIRS was abandoned as a diagnostic criterion for sepsis. However, the definition of sepsis continues to be problematic, as explained next.

A Better Definition

The presence of infection is a central feature in the definition of sepsis and septic shock. However, there is often no documented infection in cases of sepsis; e.g., *in a survey of 2.5 million patients with sepsis and septic shock, there was no documented infection in 70% of the cases* (18). Since the clinical suspicion of infection in cases of sepsis is typically based on the presence of a systemic inflammatory response (fever, leukocytosis, etc.), it seems likely that *sepsis is a dysregulated host response to inflammation, not infection.*

Pathophysiology

Regardless of whether the sepsis is a dysregulated response to infection or inflammation, septic shock is distinguished from sepsis by the presence of hemodynamic instability and mitochondrial dysfunction.

Hemodynamic Alterations

The hemodynamic aberrations in septic shock are summarized below:

. The principal hemodynamic problem is hypotension from systemic vasodilation. This has been attributed to the enhanced production of nitric oxide by the vascular endothelium (24), but the inactivation of nitric oxide by oxidant stress (see Equation 17.1) suggests the involvement of

other factors.

. Oxidant injury in the vascular endothelium leads to fluid extravasation and hypovolemia, which aggravates the hypotension.

. Proinflammatory cytokines promote cardiac dysfunction (both systolic and diastolic dysfunction), but the cardiac output is usually increased as a result of tachycardia and a decrease in left ventricular afterload (from vasodilation) (25). The cardiac output begins to decline in the advanced stages of shock, which carries a poor prognosis.

. Despite the increased cardiac output, splanchnic blood flow is typically reduced in septic shock (24). This can lead to disruption of the bowel mucosa and translocation of enteric pathogens into the systemic circulation, which aggravates the problem.

Because of the high cardiac output and peripheral vasodilation, septic shock is also known as *hyperdynamic shock* or *warm shock*.

Mitochondrial Dysfunction

The organ dysfunction in sepsis and septic shock is attributed to a defect in the production of high-energy ATP molecules in mitochondria (26,27). This condition is attributed to oxidative damage in the electron transport chain (28), and to cytokine-mediated inhibition of pyruvate dehydrogenase, the enzyme that facilitates the entry of pyruvate into mitochondria (see Figure 9.5) (29). The resulting decrease in O_2 usage in mitochondria would explain the observation shown in Figure 17.3, where the PO_2 in skeletal muscle is *increased* in patients with severe sepsis (30).

The decrease in mitochondrial O_2 consumption in sepsis is not consistent with the observed increase in whole-body O_2 consumption in patients with sepsis. This discrepancy can be resolved by proposing that the increased O_2 consumption in sepsis is a reflection of the marked increase in O_2 consumption that occurs during neutrophil activation (31).

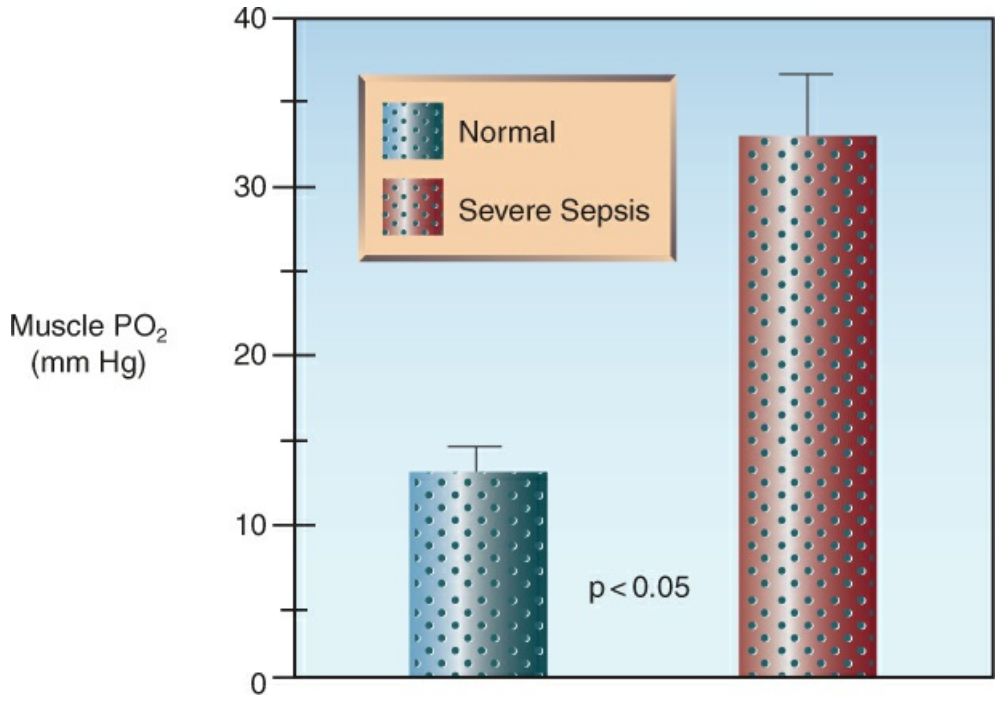

FIGURE 17.3 Direct measurements of tissue PO_2 in the forearm muscles of healthy volunteers and patients with severe sepsis. The height of the columns represents the mean value for each group, and the crossbars represent the standard error of the mean. Data from Reference 30.

IMPLICATIONS: The mitochondrial dysfunction in sepsis and septic shock has two very important implications:

- Since tissue O_2 levels are not impaired in septic shock, the liberal use of supplemental O_2 to promote tissue oxygenation is not justified, and could be harmful (by promoting oxidant stress).
- The increase in plasma lactate levels in septic shock is not the result of inadequate tissue oxygenation. Instead, the emerging paradigm is that lactate production increases during periods of metabolic stress, where lactate serves as an alternative energy source (see Table 9.6).

Monitoring

The approach to monitoring in patients with clinical shock is described in Chapter 14, but the following information about septic shock deserves mention.

- The decrease in mitochondrial O_2 usage in septic shock is associated with a decrease in O_2 extraction from the microcirculation (i.e., a decrease in the arteriovenous O_2 saturation difference) As a result, the central venous O_2 saturation ($ScvO_2$) will be inappropriately increased, and will be misleading as a measure of the adequacy of O_2 delivery. (Oxygen extraction is described in Chapter 9.)
- The PCO_2 gap is not influenced by systemic oxygenation, and can be useful for identifying tissue hypoperfusion (see Chapter 14).
- Although lactate is not a marker of anaerobic metabolism in septic shock, plasma lactate levels

have prognostic significance (see Figure 9.4), and normalization of lactate levels is an important goal of management.

Management

The initial management of septic shock is outlined in Table 17.2, using recommendations from the most recent clinical practice guidelines (32).

Volume Resuscitation

Volume infusion should be the initial intervention in any patient with a shock syndrome. The recommended fluid regimen for septic shock is 30 mL/kg (ideal body weight) of a crystalloid fluid, infused within the first 3 hours of diagnosis (32). The need for repeat fluid boluses should be guided by an assessment of fluid responsiveness (see Chapter 11).

The liberal infusion of fluids is commonplace in septic shock, but fluid accumulation has a negative impact on survival (33,34). Therefore, after the initial period of volume resuscitation, the daily infusion of fluids should be adjusted to match daily fluid losses, as this will increase the likelihood of a successful outcome.

Vasopressors

If hypotension persists after the initial volume resuscitation, infusion of a vasoconstrictor drug (vasopressor) should begin. If necessary, vasopressor infusions can begin in a peripheral vein above the antecubital fossa in the arm (32). Transition to central venous access is recommended as soon as possible, although vasopressor infusions through midline catheters have continued for 7 days without harm (35).

TABLE 17.2 The Initial Management of Septic Shock

Therapy	Recommendations†
Volume Infusion	• 30 mL/kg (ideal body weight) of a crystalloid fluid, infused within 3 hrs of presentation.
Vasopressor Therapy	• Can be initiated through a peripheral vein that is proximal to the antecubital fossa.. • Begin with norepinephrine, and titrate dose to achieve an MAP ≥65 mm Hg. • If the required dose of norepinephrine is 0.25–0.5 µg/kg/min, add vasopressin. • If necessary, add epinephrine as a 3rd vasopressor.
Corticosteroid Therapy	• If the norepinephrine dose is >0.25 µg/kg/min, give IV hydrocortisone, 50 mg every 6 hrs.
Antimicrobial Therapy	• Initiate treatment within 1 hr of presentation. • Obtain appropriate cultures prior to first dose of antibiotic.

†From Reference 32.

PREFERRED AGENTS: (*Note:* Vasopressor agents are described in Chapter 14, and Table 14.4 includes the dosing range of each agent.) *Norepinephrine is the initial vasopressor of choice in septic shock.* If the hypotension persists despite a norepinephrine dose of 0.25–0.5 µg/kg/min (18–35 µg/min in a 70 kg adult), then vasopressin should be added, and if the hypotension is refractory to norepinephrine and vasopressin, epinephrine is recommended as a third vasopressor

(32). The goal of vasopressor therapy is a mean arterial pressure (MAP) ≥65 mm Hg.

COMMENTS: The following comments about the current vasopressor recommendations deserve mention.

- Norepinephrine has immunosuppressant effects, according to studies showing that the production of proinflammatory cytokines is suppressed during norepinephrine infusions in both laboratory animal and humans (36). The clinical significance of this effect is unclear at present, but it certainly raises a red flag about the recommendation to use norepinephrine in septic shock.
- The recommendation for multiple vasopressors in vasopressor-refractory shock should be questioned, as there is no convincing evidence that the addition of vasopressin or a third vasopressor improves outcomes in septic shock (37,38).

Corticosteroids

Corticosteroids have two actions that are potentially beneficial in septic shock: they have anti-inflammatory activity, and they facilitate the vasoconstrictor response to catecholamines. However, innumerable studies since the 1960s have failed to produce convincing evidence that corticosteroids improve outcomes in septic shock (39). Yet steroids continue to be popular in septic shock, as shown by the following recommendation from the most recent guidelines on septic shock (32), which is based on a single meta-analysis showing that corticosteroids hastened the resolution of septic shock (by 1.5 days), but without improving the survival rate (40).

- Corticosteroid therapy is suggested for patients with septic shock who are receiving norepinephrine or epinephrine at a dose ≥0.25 μg/kg/min.
- The recommended regimen is IV hydrocortisone in a dose of 50 mg every 6 hours (200 mg daily). There is no recommendation for the duration of treatment, but most clinical studies use a treatment period of about 7 days.

The love affair with corticosteroids in septic shock continues.

Antimicrobial Therapy

Prompt initiation of antimicrobial therapy is considered a cornerstone of management in septic shock. The current recommendation is that *antimicrobial therapy should begin within 1 hour of presentation* (32). This doesn't leave much time to identify an infection, but it is important to obtain appropriate cultures (blood, urine, etc.) prior to the first dose of antimicrobial agent.

BLOOD CULTURES: At least 2 sets of blood cultures are recommended, using two separate venipuncture sites (one set can be obtained from an indwelling catheter). Two sets of blood cultures will detect about 90% of bloodstream infections, while 3 sets will detect close to 98% of bloodstream infections (41). The yield from blood cultures is influenced by the volume of blood that is cultured, and a volume of at least 20 mL is recommended for each set of blood cultures (42).

EMPIRIC COVERAGE: Empiric antibiotic coverage should have a broad spectrum of activity (e.g.,

piperacillin/tazobactam), and coverage for methicillin-resistant *Staphylococcus aureus* (MRSA) (with vancomycin or daptomycin) should be added if the patient has a prior history of MRSA infections, or MRSA infections are prevalent in the hospital. This can be discontinued if all cultures are negative for MRSA, including a nasal swab. If infection with a multidrug-resistant organism is suspected, empiric therapy should include two antimicrobial agents with gram-negative coverage (e.g., cefepime plus piperacillin/tazobactam). Antibiotics should be discontinued if all cultures are negative and there is no other evidence of infection (32).

Goals

The immediate goals of management are similar to the ones described for clinical shock in Chapter 14 (see Table 14.5). These goals include improvements in tissue perfusion (e.g., PCO_2 gap <6 mm Hg) and in end-organ function (e.g., increase in urine output to >0.5 mL/kg/hr), and normalization of the plasma lactate level (<2 mmol/L).

TOXIC SHOCK SYNDROME

Toxic shock syndrome (TSS) is a specialized form of septic shock that is caused by toxin-producing strains of *Staphylococcus aureus* and *Streptococcus pyogenes* (group A streptococci), and is characterized by rapidly progressive multiorgan failure. There are differences in the TSS associated with staphylococci and streptococci, and these are shown in Table 17.3.

Pathogenesis

The toxins released by the responsible microbes are capable of activating T-cell lymphocytes on a massive scale, creating a “cytokine storm” that is capable of widespread inflammatory injury. The culmination of this process is multiorgan failure and disseminated intravascular coagulopathy (DIC).

The hemodynamic changes in TSS are similar to those in septic shock, with hypotension as a result of systemic vasodilation . Disruption of the endothelium is pronounced in TSS, and the resulting fluid extravasation can lead to profound hypovolemia.

Staphylococcal TSS

Staphylococcal TSS can arise from colonization or invasive infection, and the responsible organism can be methicillin-sensitive or methicillin-resistant organisms (although the former is more frequently involved). About 40% of cases occur during menstruation (43), presumably as a result of vaginal colonization with toxin-producing staphylococci, combined with disruption of the vaginal mucosa from tampon use. Non-menstrual cases can arise from soft tissue infections such as surgical wound infections and subcutaneous abscesses. There is no identifiable infection in about 35% of cases (44).

Streptococcal TSS

Streptococcal TSS is a complication of invasive group A streptococcal infections, most notably necrotizing fasciitis, myositis, and postpartum sepsis (puerperal fever). There is no identifiable infection in almost half of the cases (45).

TABLE 17.3	Comparative Features of the Toxic Shock Syndromes	
Feature	**Staphylococcal TSS**	**Streptococcal TSS**
Notable Sources	Menstruation (tampons)Surgical wounds No source (35%)	Necrotizing fasciitis Postpartum sepsis No source (45%)
Positive Blood Cultures	<5% of cases	60% of cases
Antibiotic Therapy	MSSA: cefazolin + clindamycin MRSA: vancomycin + clindamycin	High-dose penicillin + clindamycin
Mortality Rate	Menstrual TSS: <2% Nonmenstrual TSS: 6%	35%

From References 43,46, and 47.

Clinical Presentation

TSS typically begins with an influenza-like illness (i.e., fever, myalgias, lethargy), often associated with diarrhea and a diffuse erythematous rash (resembles a sunburn) that involves the palms and soles. (Desquamation of the skin appears after 2 to 3 weeks.) This progresses within 48 hours to hypotension and involvement of multiple organs that can include the central nervous system (altered mentation) lungs (acute respiratory distress syndrome), kidneys (acute kidney injury), liver (elevated transaminases and bilirubin), skeletal muscle (rhabdomyolysis) and the hematopoietic system (DIC). Cyanosis of the distal extremities can appear, and fluid extravasation through leaky capillaries can produce nonpitting edema.

Soft tissue infections involving group A streptococci can produce severe pain (usually in the limbs, abdomen, or pelvis) without associated findings on physical examination. Pain that is out of proportion to the physical exam should raise suspicion for a deep-seated streptococcal infection.

Diagnosis

Any case of septic shock associated with an erythematous rash and rapid-onset multiorgan failure should raise suspicion for TSS, especially if there is an association with menstruation or pregnancy. However, the rash in TSS can be subtle and fleeting (46), and TSS can be mistaken for a severe case of septic shock with multiorgan failure.

Blood cultures are positive in only 5% of cases of staphylococcal TSS (43), so the diagnosis relies heavily on an association with menstruation, and any evidence of a staphylococcal infection (e.g., subcutaneous abscesses). Blood cultures have a higher yield in streptococcal TSS, and are positive in about 60% of cases (43). In cases where a streptococcal soft tissue infection is suspected, magnetic resonance imaging (MRI) can help to uncover a covert fasciitis, and bedside ultrasound is a suitable alternative for patients that are too unstable for transport to the MRI suite.

Management

The hemodynamic management of TSS is similar to that described for septic shock, with aggressive volume resuscitation followed by vasopressors if needed. Most patients with TSS also require intubation and mechanical ventilation (47).

Antimicrobial Therapy

The rapidly progressive nature of TSS emphasizes the need for rapid initiation of antibiotic therapy. Empiric antibiotic coverage should include a broad-spectrum agent (e.g., piperacillin/tazobactam or meropenem) and enhanced gram-positive coverage with vancomycin, plus clindamycin (46). The latter agent is used in all cases of TSS because of its ability to inhibit toxin production (48). Targeted antibiotic therapy for staphylococcal and streptococcal TSS is shown in Table 17.3.

Source Control

Removing the primary source is an important component of the management of TSS. For staphylococcal TSS, this includes removing tampons and intrauterine devices, eradicating nasal colonization, and draining any identified abscesses. For streptococcal TSS, debridement of necrotizing soft tissue infections is imperative for a successful outcome.

Outcomes

Most patients survive staphylococcal TSS: the mortality rate is <2% in cases associated with menstruation, and 6% in nonmenstrual cases (46). Streptococcal TSS has far fewer survivors, with a mortality rate of 35% (47).

ANAPHYLAXIS

Anaphylaxis is an acute multiorgan dysfunction syndrome produced by the immunogenic release of inflammatory mediators from basophils and mast cells. The characteristic feature is an exaggerated immunoglobulin E (IgE) response to an external antigen; i.e., a *hypersensitivity reaction*. These reactions typically involve the skin, lungs, gastrointestinal tract, and cardiovascular system, and common triggers include drugs (especially antimicrobial agents), food, and insect bites. Contrary to popular perception, deaths from anaphylaxis are rare, with a mortality rate of 0.25%–0.33% (49).

Clinical Features

Anaphylactic reactions typically appear within minutes of exposure to an external trigger, and they can recur within 72 hours of the initial episode (biphasic anaphylaxis) (49). A characteristic feature of these reactions is edema and swelling in the involved organ, which is the result of an increase in vascular permeability. The clinical manifestations of anaphylactic reactions are shown in Table 17.4 (50). Common manifestations include urticaria, subcutaneous angioedema (typically involving the face), flushing, angioedema of the upper airway (e.g., laryngeal edema) and bronchospasm. The most feared manifestation is hypotension (i.e., anaphylactic shock), and the most overlooked manifestation is an acute coronary syndrome (see next).

TABLE 17.4 Signs and Symptoms of Anaphylaxis	
Manifestation	**Frequency of Occurence**
Urticaria and angioedema	60–90%
Upper airway angioedema	50–60%
Flushing	45–55%
Dyspnea, wheezing	45–50%
Hypotension, syncope	30–35%
Abdominal pain, diarrhea	25–30%
Acute Coronary Syndrome	4–5%

From Reference 50.

Allergic Coronary Insufficiency

The association of anaphylaxis and acute coronary syndromes (the Kounis Syndrome) is attributed to coronary vasospasm (in 73% of cases), coronary artery plaque rupture (in 22% of cases) and coronary stent thrombosis (in 5% of cases) (51). The presumed mechanisms include the release of vasoactive substances from mast cell degranulation, and platelet activation. Coronary vasospasm is the most common underlying mechanism, and occurs predominantly in younger patients with no history of coronary artery disease. Cardiac symptoms usually appear within one hour of the anaphylactic reaction (e.g., urticaria, angioedema, bronchospasm), and can include fleeting chest pains (from coronary spasm) or ST-elevation myocardial infarction (from plaque rupture or stent thrombosis).

Treatment

The treatment of anaphylaxis includes one drug that halts the reaction (epinephrine), and drugs that alleviate symptoms (antihistamines, bronchodilators).

Epinephrine

Epinephrine blocks the release of inflammatory mediators from sensitized basophils and mast cells, and is *the only drug capable of stopping an anaphylactic reaction* (50). It is available in a confusing array of aqueous solutions, which are shown in Table 17.5. The optimal epinephrine dose for anaphylaxis is unknown, but the usual dose in adults is 0.3–0.5 mg (0.3–0.5 mL of 1:1000 solution) given by deep intramuscular (IM) injection in the anterolateral thigh, and repeated every 5–15 minutes if necessary (50). Drug absorption is slower with subcutaneous injection (52). Epinephrine can be nebulized for laryngeal edema using the dosing regimen in Table 17.5, but the efficacy of this regimen is unclear.

TABLE 17.5 Aqueous Epinephrine Solutions and Their Clinical Uses		
Aqueous Dilution	**Condition**	**Dosing Regimen**

1:100 (10 mg/mL)	Laryngeal Edema	0.25 mL (2.5 mg) in 2 mL saline and administer by nebulizer.
1:1,000 (1 mg/mL)	Anaphylaxis	0.3–0.5 mL (mg) by deep IM injection in the thigh every 5–15 min as needed.
1:10,000 (0.1 mg/mL)	Asystole or PEA	10 mL (1 mg) IV every 3–5 min as needed.
1:100,000 (10 µg/mL)	Anaphylactic Shock	Add 2 mL of 1:1000 solution (2 mg) to 200 mL saline (10 µg/mL) and infuse at 5–15 µg/min.

From Reference 53.

GLUCAGON: The inhibitory actions of epinephrine on mast cell degranulation are mediated by β-adrenergic receptors, and ongoing therapy with β-receptor antagonists can attenuate or eliminate the response to epinephrine. When anaphylactic reactions are refractory to epinephrine in patients receiving β-blocker drugs, glucagon can be effective in restoring responsiveness (for reasons described in Chapter 52). The dose of glucagon is 1–5 mg by slow intravenous injection (over 5 min), followed by a continuous infusion at 5–15 µg/min, titrated to the desired response (53). Glucagon can trigger vomiting, and patients with depressed consciousness should be placed on their side when glucagon is administered, to limit the risk of aspiration.

Second-Line Agents

The following drugs are used for symptom relief, and do not alter the course of the illness. They are given after epinephrine is administered, and should never be used as a replacement for epinephrine.

ANTIHISTAMINES: Histamine receptor antagonists are used to relieve the pruritis and rhinorrhea associated with anaphylactic reactions (although their efficacy is unproven). The histamine H_1 blocker *diphenhydramine* (25–50 mg PO, IM, or IV) and the histamine-H_2 blocker *ranitidine* (50 mg IV or 150 mg PO) are considered equivalent in efficacy, but combination therapy produces the best results (54).

BRONCHODILATORS: Inhaled β_2 -receptor agonists like *albuterol* are used to relieve bronchospasm, and are administered by nebulizer (2.5 mL of a 0.5% solution) or by metered-dose inhaler (54).

Corticosteroids

Corticosteroids have enjoyed a longstanding popularity in the treatment of hypersensitivity reactions, and they are sometimes preferred to epinephrine for the acute management of anaphylaxis (54). However, there is no evidence that corticosteroids are effective in reversing, slowing, or preventing the recurrence of anaphylactic reactions (49,50,54). This is reflected in the following statement from a clinical practice guideline on anaphylaxis (50): "*The use of corticosteroids has no role in the acute management of anaphylaxis*".

Anaphylactic Shock

Anaphylactic shock is characterized by the same hemodynamic abnormalities described earlier

for septic shock, but the hypotension in anaphylactic shock can be more pronounced because of the exaggerated fluid loss through leaky capillaries. Management includes intravenous epinephrine and aggressive volume resuscitation.

Epinephrine

There is no standardized dosing regimen for epinephrine in anaphylactic shock, but the dose rate of 5–15 μg/min in Table 17.5 has been cited for its efficacy (53). A bolus dose of 10 μg IV can precede the drug infusion, and can be repeated periodically if needed to maintain the mean arterial pressure at ≥65 mm Hg (54).

Volume Resuscitation

Aggressive volume resuscitation is essential in anaphylactic shock because as much as 35% of the intravascular volume can be lost through leaky capillaries (53), which is enough to produce hypovolemic shock (see Table 15.1). Volume resuscitation can begin by infusing 1–2 liters of a crystalloid fluid (or 20–30 mL/kg), or 500 mL of 5% albumin, over the first 5–10 minutes (53). Thereafter, fluid management should be tailored to the clinical condition of the patient. Considering adding a colloid fluid (e.g., 5% albumin) to your volume regimen, since the severity of the capillary leak in anaphylactic shock will ensure that most of the infused crystalloid fluid will move out of the vascular compartment and add to the edema.

Refractory Hypotension

For hypotension that persists despite epinephrine and volume resuscitation, give glucagon if the patient has received a β blocker recently. Otherwise, add a second vasopressor like norepinephrine or phenylephrine (vasopressin has not been evaluated in anaphylactic shock). The prognosis in this situation is poor.

A FINAL WORD

Inflammation (not hypoxia) as the Major Cause of Death in ICUs

The following information is a spinoff of the information presented in A FINAL WORD in Chapter 9, which is titled “Is cellular hypoxia a common cause of death?” The observations presented in this chapter, which are summarized in the statements below, provide evidence that inflammation, not cellular hypoxia, is the most common cause of death in the hospital.

. Septic shock is the leading cause of in-hospital deaths in the United States (16).

. The source of organ failure in septic shock is mitochondrial dysfunction, not inadequate tissue oxygenation (see Figure 17.3), and the source of the mitochondrial dysfunction is inflammation.

The apparent role of inflammation in fatal outcomes creates doubt about the emphasis on promoting tissue oxygenation (e.g., with O_2 inhalation and RBC transfusions) in critically ill patients. In fact, since the damaging effects of inflammation are largely due to oxidation, promoting tissue oxygenation may have an effect that is diametrically opposed to what is

intended. More on this in Chapter 25 (Oxygen Therapy).

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Section VII

CARDIAC DISORDERS

Nothing is so firmly believed as that which is least known.

Francis Jeffrey
(1773–1850)

Chapter 18

Acute Heart Failure(s)

Movement is the cause of all life.

Leonardo da Vinci

Despite the emphasis on a “heart healthy” lifestyle in modern times, heart failure has grown in prevalence and associated mortality in recent years; i.e., the number of adults in the United States with heart failure increased from 6 million in 2018 to 6.7 million in 2020, and deaths attributed to heart failure were 50% higher in 2020 than in 2010 (1). Current surveys show that one of every 8 deaths in the United States is related to heart failure (1), indicating that heart failure is a leading health problem in this country.

Heart failure is not a single entity (as the title suggests), and is classified according to the portion of the cardiac cycle that is affected (systole or diastole) and the side of the heart that is involved. This chapter describes each type of heart failure, and focuses on the acute, decompensated stage of heart failure that requires management in the hospital. (*Note:* This chapter does not include cardiogenic shock, which is described in Chapter 16.) Many of the recommendations in this chapter are borrowed from the clinical practice guidelines listed at the end of the chapter (2–5).

TYPES OF HEART FAILURE

Heart failure can be the result of impaired cardiac filling (diastolic dysfunction) or a decrease in contractile strength (systolic dysfunction), and these abnormalities can predominate in the left or right side of the heart.

Systolic vs. Diastolic Dysfunction

The influence of systolic and diastolic dysfunction on measures of cardiac performance are shown in Figure 18.1. The upper graph shows the relationship between ventricular end-diastolic pressure (EDP) and stroke volume (which are known as “ventricular function curves"). The curve representing heart failure has a decreased slope, and the point on the curve indicates that heart failure is associated with an increase in EDP and a decrease in stroke volume. The lower graph shows the relationship between ventricular end-diastolic pressure and end-diastolic volume

(EDV). The curve representing diastolic dysfunction has a decreased slope, which reflects a decrease in ventricular compliance (distensibility) according to the following relationship:

$$\text{Compliance} = \Delta EDV/\Delta EDP \tag{18.1}$$

The points on the ventricular compliance curves indicate that the increase in EDP in heart failure is associated with an increase in EDV if the problem is systolic dysfunction, and a decrease in EDV if the problem is diastolic dysfunction. Therefore, *the end-diastolic volume (not the end-diastolic pressure) can distinguish between systolic and diastolic dysfunction in patients with heart failure*. An end-diastolic volume of 97 mL/m^2 (measured relative to body surface area in m^2) is used to distinguish between systolic and diastolic dysfunction i.e., an EDV >97 mL/m^2 indicates systolic dysfunction, and an EDV ≤97 mL/m^2 indicates diastolic dysfunction (6). Because EDV is not easily measured at the bedside, the "ejection fraction" is used to distinguish between systolic and diastolic dysfunction (see next).

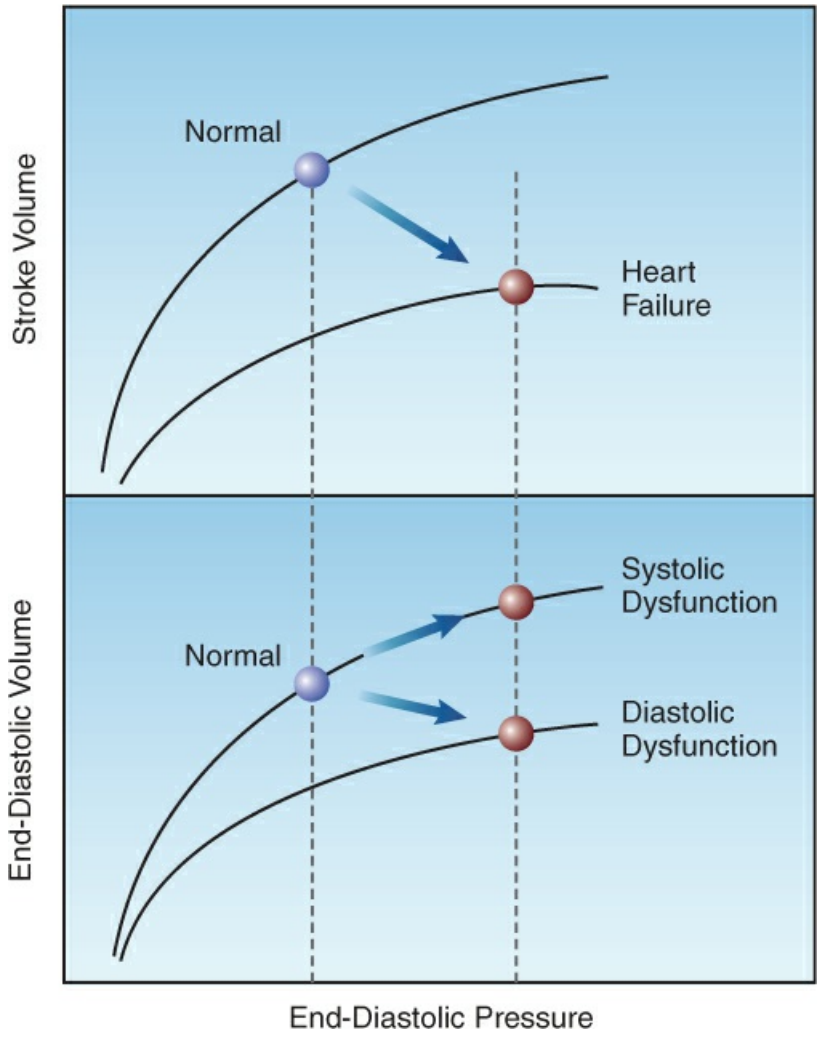

FIGURE 18.1 Graphs showing the influence of systolic and diastolic dysfunction on measures of cardiac performance. Upper panel shows ventricular function curves, and lower panel shows diastolic pressure-volume curves. See text for explanation.

Ejection Fraction

The fraction of the ventricular volume that is ejected during systole is called the *ejection fraction* (EF), and is the ratio of stroke volume (SV) to end-diastolic volume (EDV):

$$EF = (SV/EDV) \times 100 \quad (18.2)$$

(The ratio is multiplied by 100 to express it as a percentage.) The EF is directly related to the strength of ventricular contraction, and is used a measure of systolic function. The normal EF of the left ventricle is ≥55%, but a lower value of ≥50% is used as normal in patients with heart failure because increases in afterload can reduce the EF by 5–10% (2).

The classification of left heart failure based on the left-ventricular ejection fraction (LVEF) is shown in Table 18.1 (2).

. Heart failure caused by diastolic dysfunction has a normal LVEF (≥50%), and is called *heart failure with preserved ejection fraction* (HFpEF).

. Heart failure caused by systolic dysfunction has a reduced LVEF (<50%), and is subdivided into *heart failure with mildly reduced ejection fraction* (HFmrEF) if the LVEF is 41–49%, and *heart failure with reduced ejection fraction* (HFrEF) if the LVEF is ≤40%.

TABLE 18.1 Classification of Heart Failure Based on Left Ventricular Ejection Fraction (LVEF)

Category	LVEF	Problem
Heart Failure with preserved ejection fraction (HFpEF)	≥50%	Diastolic Dysfunction
Heart Failure with mildly reduced ejection fraction (HFmrEF)	41–49%	Systolic Dysfunction (mild)
Heart Failure with reduced ejection fraction (HFrEF)	≤40%	Systolic Dysfunction (moderate/severe).

From the clinical practice guidelines in Reference 2.

Diastolic Dysfunction

Early descriptions of heart failure attributed most cases to systolic dysfunction, but diastolic dysfunction is now recognized as a cause of at least 50% of cases of left heart failure (2). The functional problem with diastolic dysfunction is a decrease in ventricular distensibility that impairs ventricular filling during diastole. The result is a decrease in end-diastolic volume (EDV), and although the EF is preserved, the stroke volume is reduced because the EF is a fraction of a lower EDV.

Common causes of heart failure with preserved EF (HFpEF) include ventricular hypertrophy, myocardial ischemia (stunned myocardium), restrictive (fibrotic) cardiomyopathy, and pericardial tamponade. High intrathoracic pressures during mechanical ventilation can also impair ventricular filling and aggravate HFpEF.

Right Heart Failure

Right-sided heart failure is usually a consequence of pulmonary hypertension (e.g., from pulmonary emboli or chronic lung disease) or inferior wall myocardial infarction. The principal

mechanism is systolic dysfunction, and the result is an increase in right-ventricular end-diastolic volume (RVEDV). This can be difficult to detect clinically because the central venous pressure (CVP) does not rise (and jugular venous distension does not occur) until the increase in RVEDV is restricted by the pericardium (*pericardial constraint*) (7).

Echocardiography

Transthoracic echocardiography (TTE) is the standard method for detecting right heart failure at the bedside. An example of a 2D ultrasound image showing right heart failure is shown in Figure 18.2 (7). This is a parasternal short-axis view showing right ventricular enlargement. The right ventricular (RV) cavity is normally about two-thirds the size of the left ventricular (LV) cavity (8), and the image in Figure 18.2 shows that the RV cavity is larger than the LV cavity. Note also that the interventricular septum flattens during diastole, which is a sign of volume overload in the right ventricle. Further distension of the right ventricle will push the interventricular septum towards the left ventricle and reduce the size of the left ventricular chamber. This septal displacement impairs left ventricular filling and increases the left ventricular end-diastolic pressure. In this way, *right-sided heart failure can produce diastolic dysfunction in the left ventricle* by the process known as *interventricular interdependence*.

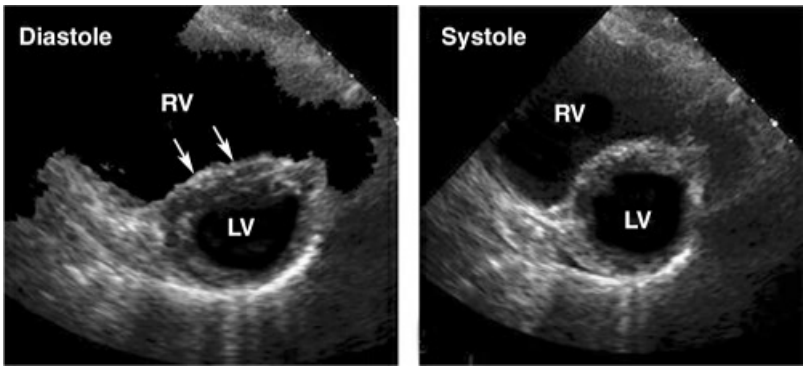

FIGURE 18.2 Transthoracic ultrasound image in the parasternal short-axis view showing right ventricular (RV) enlargement, where the RV cavity is larger than the left ventricular (LV) cavity. Note also that the interventricular septum is flattened during diastole (indicated by the arrows), which is a sign of RV volume overload. Image retouched from Reference 9.

Quantitative measurements of RV chamber size and fractional shortening are also available for the diagnosis of RV failure (9), but measurements obtained with 2D echocardiography are prone to errors because of alterations in the normal RV geometry, and interobserver differences in probe positioning. 3D echocardiography overcomes the problem with altered RV geometry, and provides measures of RVEDV and RVEF (normal RVEF >45%) (10). However, the most accurate measures of RV size and systolic function are provided by cardiac magnetic resonance imaging (not covered here).

Cardiac Filling Pressures

When a pulmonary artery catheter is in place, right heart failure is a consideration if the CVP is equal to, or greater than, the pulmonary artery wedge pressure (PAWP) (11). However, equalization of the CVP and PAWP also occurs with pericardial tamponade, so echocardiography is needed to identify which condition is present.

CARDIOVASCULAR CONSEQUENCES

The physiological and clinical consequences of heart failure are the result of venous congestion and a reduction in forward flow. The extent to which these derangements occur depends on the stage of heart failure, as described next.

Progressive Stages of Heart Failure

The changes in cardiac performance that occur in progressive stages of left heart failure are shown in Figure 18.3. Three distinct stages are identified, and each is summarized below (using the corresponding numbers in Figure 18.3).

. The earliest sign of ventricular dysfunction is an increase in end-diastolic filling pressure (i.e., the pulmonary artery wedge pressure). The stroke volume is maintained, but at the expense of the elevated filling pressure, which produces venous congestion in the lungs and the resulting sensation of dyspnea.

. The next stage is marked by a decrease in stroke volume and an increase in heart rate. The tachycardia offsets the reduction in stroke volume, so the cardiac output is preserved.

. The final stage is characterized by a decrease in cardiac output and a further increase in the ventricular filling pressure. The point at which the cardiac output begins to fall marks the transition from compensated to decompensated heart failure.

Neurohumoral Responses

Heart failure triggers a multitude of endogenous responses, some beneficial and some counterproductive. The following responses have the most clinical relevance (12).

Natriuretic Peptides

Increases in atrial and ventricular wall tension are accompanied by the release of four structurally similar *natriuretic peptides* from cardiac myocytes. These peptides “unload” the ventricles by promoting sodium excretion in the urine (which reduces ventricular preload) and dilating systemic blood vessels (which reduces ventricular preload and afterload). Natriuretic peptides are also used as diagnostic markers for heart failure, as described later.

Sympathetic Nervous System

Decreases in stroke volume are sensed by baroreceptors in the carotid and pulmonary arteries, and activation of these receptors results in brainstem activation of the sympathetic nervous system. This occurs in the early stages of heart failure, and the principal results are positive inotropic and chronotropic effects in the heart, peripheral vasoconstriction, and activation of the renin-angiotensin-aldosterone system.

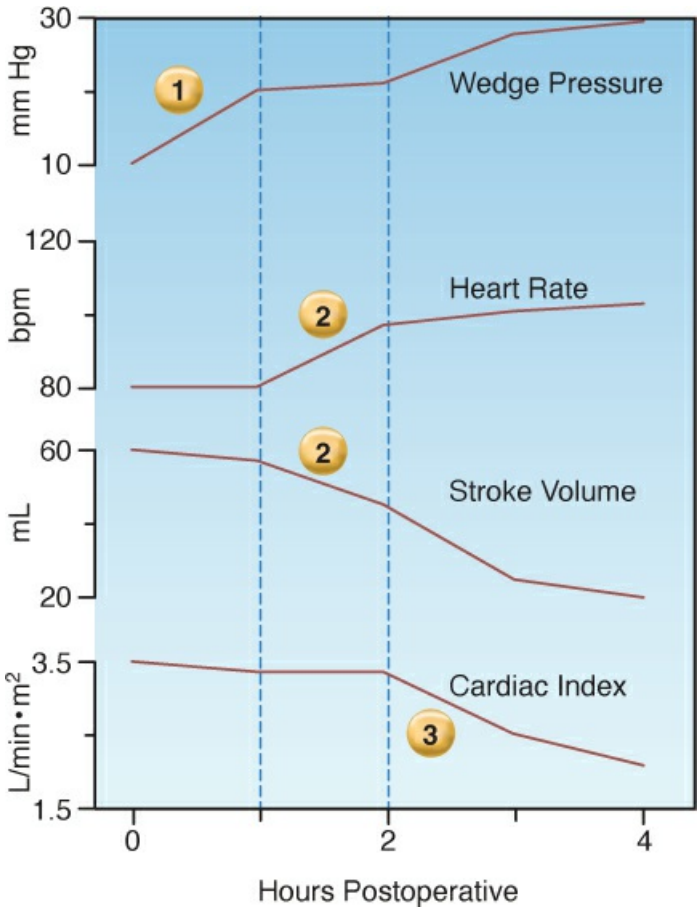

FIGURE 18.3 Changes in cardiac performance during progressive stages of left-sided heart failure in a postoperative patient. Data from personal observations. See text for further explanation.

Renin-Angiotensin-Aldosterone System

Specialized cells in the renal arterioles release renin in response to renal hypoperfusion and adrenergic β-receptor stimulation. Renin release has three consequences: the formation of angiotensin II, the production of aldosterone in the adrenal cortex, and the (angiotensin-triggered) release of arginine vasopressin from the posterior pituitary. Angiotensin produces systemic vasoconstriction, while aldosterone promotes renal sodium and water retention, and vasopressin promotes both vasoconstriction and renal water retention. Angiotensin also helps to preserve the glomerular filtration in the kidneys by vasoconstricting the arterioles on the efferent side of the glomerulus, which increases the filtration pressure across the glomerulus.

Activation of the renin-angiotensin-aldosterone (RAA) system can be counterproductive in the advanced stages of heart failure, when the vasoconstriction can impede systemic blood flow, and the renal retention of sodium and water can promote unwanted (especially pulmonary) edema.

Venous Congestion

Although decompensated heart failure is associated with a decrease in cardiac output, peripheral vasoconstriction is usually sufficient to maintain blood pressure and tissue perfusion. As a result,

the principal manifestations of acute, decompensated heart failure are related to venous congestion (13). The following are two of the more serious consequences of venous congestion.

Pulmonary Edema

The clinical presentation of acute heart failure is dominated by complaints of dyspnea and evidence of pulmonary congestion (i.e., basilar crackles on lung auscultation, chest x-ray changes, and hypoxemia). The chest x-ray may show minimal changes, or it may show evidence of pulmonary edema. The chest film in Figure 18.4 shows the classic appearance of "cardiogenic" pulmonary edema, with infiltrates spreading out from the hilar regions bilaterally. Pleural effusions are also commonplace with cardiogenic pulmonary edema. (For a comparison with "noncardiogenic pulmonary edema", see Chapter 24).

Cardiorenal Syndrome

Heart failure is often accompanied by renal insufficiency, which had been attributed to a reduction in cardiac output. However, there is no correlation between cardiac output and renal dysfunction in patients with heart failure (14), and renal autoregulation typically maintains renal blood flow until the mean arterial pressure drops below 70 mm Hg (15). Observations like these have led to the notion that *the renal dysfunction in acute heart failure is primarily the result of increased venous pressure* (which impairs glomerular blood flow by reducing the renal arteriovenous pressure gradient), and that a low cardiac output plays a role only in patients with hypotension (i.e., cardiogenic shock). This new entity (where venous congestion links heart failure and renal failure) is known as the *cardio-renal syndrome* (5,16), and the principal treatment is diuresis.

Biomarkers

Plasma levels of natriuretic peptides are recommended in patients who present with signs of acute heart failure (2). The principal peptide that is assayed is brain-type or B-type natriuretic peptide (BNP), which is released as a prohormone (proBNP) from both ventricles in response to increased wall tension. The prohormone is cleaved to form BNP (the active hormone) and N-terminal (NT)-proBNP, which is metabolically inactive. The clearance of BNP and NT-proBNP is primarily via the kidneys. However, peptide receptors in adipose tissue also contribute to peptide clearance (17), which may explain why plasma BNP and NT-proBNP levels are lower in obese patients (2). NT-proBNP has a longer half-life than BNP, resulting in plasma levels that are 3–5 times higher than BNP levels.

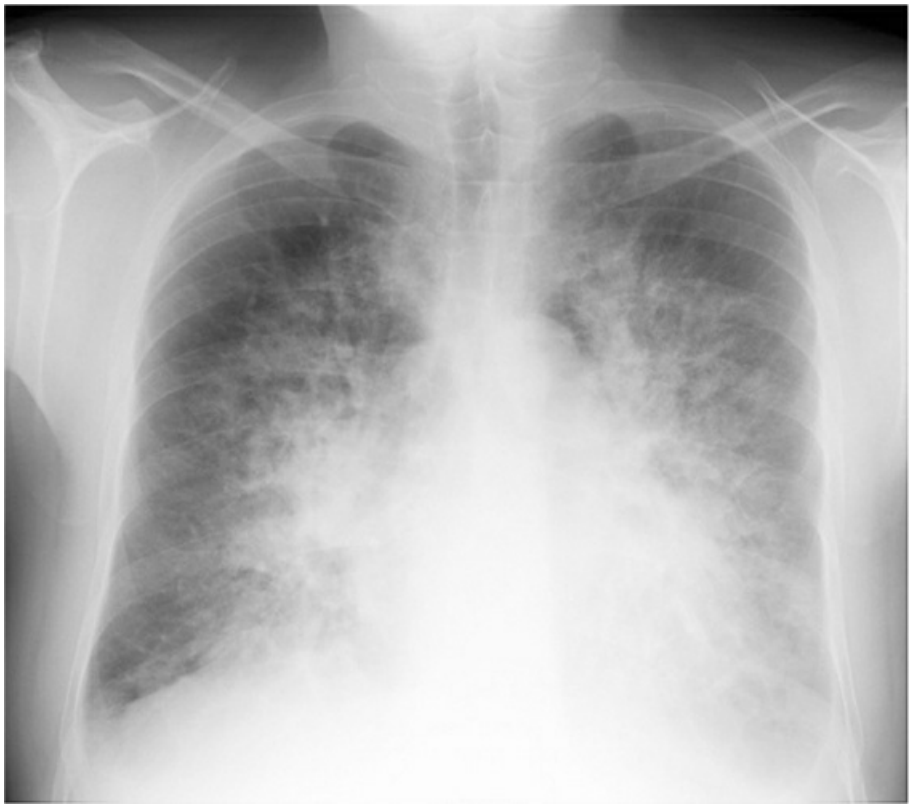

FIGURE 18.4 Portable chest x-ray in a patient with acute heart failure and pulmonary edema. Note that the infiltrates radiate out from the hilar regions, which is a feature that distinguishes cardiogenic from noncardiogenic pulmonary edema.

TABLE 18.2 Causes of Elevated Natriuretic Peptide Levels

Cardiac	Noncardiac
Heart failure (R and L)	Advanced Age
Myocarditis	Renal Failure
Ventricular Hypertrophy	Anemia
Acute Coronary Syndromes	Pulmonary Embolism
Pericardial Disease	Pulmonary Hypertension
Atrial Fibrillation	Bacterial Sepsis
Cardioversion	Critical Illness
Cardiac Surgery	

From Reference 2.

Diagnostic Value

Heart failure is unlikely if BNP levels are <100 picograms/mL (18,19), or NT-proBNP levels are <300 picograms/mL (20). However, there are several conditions other than heart failure that can elevate natriuretic peptide levels, as shown in Table 18.2. Because of the nonspecific nature of elevated peptide levels (especially in critically ill patients), *natriuretic peptide levels are better suited for excluding the presence of heart failure* (2).

MANAGEMENT STRATEGIES

The management described here is for acute left-sided heart failure that does not result in cardiogenic shock; i.e., is not associated with hypotension or elevated plasma lactate levels. (The management of cardiogenic shock is described in Chapter 16.) As mentioned earlier, this condition typically presents with signs and symptoms related to pulmonary venous congestion. The initial approach is dictated by the blood pressure.

High Blood Pressure

Hypertension is common in acute heart failure (2), and is often a secondary phenomenon (e.g., from agitation, hypoxemia, etc.), but occasionally is the primary problem (e.g., hypertensive emergency). In this situation, management begins with infusion of a vasodilator like the ones in Table 18.3 (2,21).

Vasodilators

The vasodilators in Table 18.3 are capable of dilating both arteries and veins, and will decrease both ventricular preload and afterload. The decrease in preload reduces venous congestion in the lungs, and the decrease in afterload promotes cardiac output. The overall effect is a decrease in arterial blood pressure, an increase in cardiac output, and a decrease in hydrostatic pressure in the pulmonary capillaries.

TABLE 18.3 Vasodilator Infusions for Acute Heart Failure

Agent	Dosing Recommendations
Nitroglycerin	1. Start infusion at 5 µg/min, and increase by 5 µg/min every 5 min to achieve the desired effect. The effective dose is 5–100 µg/min, in most cases, and doses above 200 µg/min are not advised. 2. Tachyphylaxis is common after 24 hrs, and propylene glycol toxicity is a risk with prolonged infusions. 3. Very high doses of nitroglycerin can promote methemoglobinemia.
Nitroprusside	1. Start infusion at 0.2 µg/kg/min and titrate upward every 5 min to achieve the desired effect. The effective dose is 2–5 µg/kg/min in most cases, and the maximum dose allowed is 10 µg/kg/min. 2. To reduce the risk of cyanide toxicity, avoid prolonged infusions at >3 µg/kg/min, and do not use the drug in patients with renal or hepatic insufficiency. Thiosulfate (500 mg) can be added to the infusate to bind the cyanide released from nitroprusside. 3. Not recommended for heart failure associated with coronary ischemia (see text for explanation).

NITROGLYCERIN: Nitroglycerin is the vasodilator of choice for hypertensive acute heart failure (2). The drug binds to soft plastics like polyvinylchloride (PVC), which is a common constituent of the plastic bags and tubing used for intravenous infusions. *As much as 80% of nitroglycerin can be lost to adsorption in PVC-based infusion systems* (22), so it is imperative to use glass bottles and polyethylene tubing when infusing nitroglycerin.

Infusions of nitroglycerin should not continue for longer than 24 hours, because *tachyphylaxis* is common after 24 hours of continuous infusion (2). Prolonged infusions of nitroglycerin can also produce *propylene glycol toxicity* (23), which is characterized by lactic

acidosis, delirium, hypotension, and multiorgan failure in severe cases (24), and is a result of the propylene glycol used as a solvent to promote the water solubility of intravenous nitroglycerin. Finally, very high doses of nitroglycerin can produce *methemoglobinemia*, due to the breakdown of nitroglycerin to nitrite ions, which can oxidize hemoglobin to form methemoglobin (25). However, this almost never occurs during therapeutic drug dosing.

NITROPRUSSIDE: About 20% of patients with acute heart failure are resistant to nitroglycerin (2), and in this situation, nitroprusside is available as an alternate vasodilator. Unfortunately, the nitroprusside molecule contains 5 cyanide atoms, and release of the cyanide during nitroprusside breakdown can lead to life-threatening *cyanide intoxication* (26). Both the liver and kidneys participate in cyanide clearance, and thus *nitroprusside is not recommended in patients with renal or hepatic insufficiency*. Thiosulfate binds cyanide and reduces the risk of cyanide toxicity (26), and sodium thiosulfate can be added to nitroprusside infusions as a preventive measure (see Table 18.3).

Nitroprusside has an additional risk in patients with ischemic heart disease because it can produce a *coronary steal syndrome* by diverting blood flow away from ischemic regions of the myocardium (27). Because of this risk, *nitroprusside is not recommended in patients with ischemic heart disease.*

Diuretics

Acute treatment with an intravenous diuretic (described later) is considered only after vasodilator therapy has normalized the blood pressure, *and* there is continued evidence of venous congestion. The most popular diuretic, *intravenous furosemide, produces an acute vasoconstrictor response* (28) by stimulating renin release and promoting the formation of angiotensin II, a potent vasoconstrictor. Because of this response, intravenous furosemide should delayed until the blood pressure is controlled with vasodilator therapy.

For patients with indwelling pulmonary artery catheters, the desired pulmonary artery wedge pressure in left heart failure is the highest pressure that will augment cardiac output without producing pulmonary edema. This pressure usually corresponds to a wedge pressure of 18 to 20 mm Hg (29). Therefore, diuretic therapy can be added if the wedge pressure remains above 20 mm Hg during vasodilator therapy. The specifics of diuretic therapy are described later.

Normal Blood Pressure

For acute heart failure with a normal blood pressure, vasodilator therapy with nitroglycerin is a consideration if there is evidence of reduced peripheral blood flow (e.g., increased PCO_2 gap). Otherwise, an intravenous diuretic (most often furosemide) is indicated, and there is evidence that *administration of a diuretic within one hour of presentation is associated with improved outcomes* (30).

Diuretic Therapy

At the outset, there are three concerns about intravenous diuretics in acute heart failure that deserve mention:

. Intravenous furosemide causes a *decrease* in cardiac output in acute heart failure (31–33). This

is the combined result of a decrease in venous return and an increase in left ventricular afterload; the latter effect being attributed to an acute vasoconstrictor response mentioned earlier (28).

- The presence of pulmonary edema in acute heart failure is not evidence of fluid overload, and could be the result of an increase in pulmonary venous pressures from ischemic myocardial "stunning" (often called "flash" pulmonary edema). Diuretics should be used cautiously in this situation.
- Diuretics should be used cautiously in acute heart failure with preserved ejection fraction (HFpEF) because there can be a decrease in cardiac filling in this form of heart failure.

Evidence of a decrease in tissue perfusion after an intravenous diuretic should prompt consideration of vasodilator therapy (e.g., with nitroglycerin) (33), and sometimes a bolus dose of intravenous fluids is advantageous in this situation.

TABLE 18.4 Diuretic Therapy for Acute Heart Failure

Agent	Dosing Recommendations
Furosemide	1. For patients who are furosemide-naïve, start with an IV dose of 40 mg (for normal renal function) or 60–80 mg (for renal impairment). 2. For patients already receiving furosemide, start with an IV dose equal to the total daily furosemide dose. 3. If response not satisfactory after 2 hrs, double the dose, and continue this, if necessary, to a maximum dose of 200 mg. 4. The effective IV dose is then given twice daily.
Bumetanide Torsemide	1. These loop diuretics have a greater bioavailability than furosemide, and can be effective in cases of furosemide resistance. 2. Dose equivalence: 40 mg furosemide = 1 mg bumetanide = 20 mg torsemide
Metolazone	1. A thiazide diuretic that can augment the effect of loop diuretics. 2. Dose is 2.5–10 mg PO daily, and should be given a few hours prior to the loop diuretic. 3. Combination therapy increases the risk of hypokalemia.

FUROSEMIDE: Furosemide is the most popular diuretic for the treatment of heart failure, and acts by blocking sodium reabsorption in the ascending loop of Henle (a "loop diuretic"). The following are some relevant points about furosemide dosing in acute heart failure. (See also Table 18.4.)

- Following an intravenous dose of furosemide, diuresis begins within 5 minutes, peaks at 20–60 minutes, and lasts 2 hours (34).
- For patients who are not on outpatient therapy with furosemide, the initial intravenous dose is 40 mg if renal function is normal. Higher doses (60–80 mg) are needed in the presence of renal insufficiency (35).
- For patients who are receiving furosemide as an outpatient, the initial IV dose should be equivalent to the total daily outpatient dose (35).

. If the diuresis is not adequate (at least 1 liter) at 2 hours after the initial dose, the dose is doubled, and this is continued until a satisfactory response is achieved, or the furosemide dose reaches 200 mg. Failure to respond to an IV dose of 200 mg is evidence of furosemide resistance.

. The effective IV dose of furosemide is then given twice daily. When the venous congestion (e.g., pulmonary edema) is no longer problematic, the drug can be given orally. Although IV and oral doses are often used interchangeably, only 50% of an oral dose of furosemide is absorbed (36), so oral dosing may need to be adjusted upwards to maintain an equivalent response.

Furosemide Resistance

Critically ill patients can have an attenuated response to furosemide, particularly with continued use. This may be the result of hypoalbuminemia (because furosemide is highly protein-bound), renal hypoperfusion, or "diuretic braking' (i.e., decreased responsiveness as hypervolemia resolves) (37). The following options are available when the diuretic response to furosemide is inadequate.

TRY ANOTHER LOOP DIURETIC: Bumetanide and torsemide are loop diuretics that have a greater bioavailability than furosemide, and will occasionally produce satisfactory diuresis in cases of furosemide resistance. For equivalent dosing, *40 mg of furosemide is equivalent to 1 mg of bumetanide or 20 mg of torsemide* (35).

ADD A THIAZIDE: Thiazide diuretics have a different mechanism of action than loop diuretics (i.e., they block sodium reabsorption in the distal renal tubules), and addition of a thiazide can augment the diuretic response to furosemide. The thiazide most favored for this purpose is *metolazone* because it retains its efficacy in renal insufficiency (37). The dose of metolazone is 2.5–10 mg daily in a single oral dose. The response to metolazone begins at one hour and peaks at 9 hours, so the metolazone dose should be given a few hours prior to the furosemide dose. One concern that deserves mention is that *combined treatment with thiazides and loop diuretics increases the risk of hypokalemia*.

Continuous-Infusion Diuretics

For patients who are massively volume-overloaded, continuous infusions of a loop diuretic can produce a more sustained diuresis than bolus drug injection (38), although this is not a consistent finding (39). The following is a dosing regimen for continuous-infusion furosemide (40):

. Start with an IV bolus dose of 80 mg.

. If the estimated GFR is ≥30 mL/1.73 m^2, start the furosemide infusion at 5 mg/hr. If this does not produce the desired response (i.e., urine output ≥100 mL/hr), give a second bolus dose and increase the infusion rate to 10 mg/hr. Thereafter, the infusion rate can be increased, if needed, to a maximum rate of 40 mg/hr.

. If the estimated GFR is <30 mL/1.73 m^2, start the furosemide infusion at 20 mg/hr. If this does not produce the desired response (i.e., urine output ≥100 mL/hr), give a second bolus dose and increase the infusion rate to 40 mg/hr.

Long-Term Therapies

The following therapies, which are outlined in Table 18.5, have shown evidence of improved long-term outcomes and reduced hospitalizations for patients with heart failure (2). *The principal benefit of these therapies is in heart failure associated with reduced ejection fraction* (HFrEF) (2), but they are also popular in cases of heart failure with preserved ejection fraction (HFpEF), if tolerated. All treatments are oral, and are started (or continued) after the acute episode has resolved, and the patient's condition has stabilized. These therapies are NOT advised for patients with hypotension or evidence of impaired tissue perfusion.

TABLE 18.5 Therapies that Improve Outcomes in Heart Failure with Reduced Ejection Fraction

Agents	Initial Dose	Target Dose
RAA Suppression:		
Sacubitril/Valsartan	24 mg/26 mg BID for normotension 49 mg/51 mg BID for hypertension	97 mg/103 mg BID
Beta Blockers:		
Carvedilol	3.125 mg BID	25–50 mg BID
Metoprolol succinate extended release	12.5–25 mg once daily	200 mg once daily
SGLT2 Inhibitors:		
Dapagliflozin or Empagliflozin	10 mg once daily	10 mg once daily
Aldosterone Antagonists:		
Spironolactone	12.5–25 mg once daily	25 mg once daily
Eplerenone	25 mg once daily	50 mg once daily

From the clinical practice guidelines in Reference 2.

RAA Suppression

Drugs that inhibit the renin-angiotensin-aldosterone (RAA) system are recommended for all patients with HFrEF (2). RAA suppressant drugs include angiotensin converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and the combination of an ARB and a neprilysin inhibitor. (Neprilysin is an enzyme that degrades natriuretic peptides.)

All RAA suppressant drugs are considered effective in improving long-term outcomes in patients with HFrEF, and may derive their benefit via left ventricular remodeling (2). *The most effective drug (at this time) is a combination drug that contains sacubitril (a neprilysin inhibitor) and valsartan (an ARB)* (2,41). The dosing regimen is shown in Table 18.5. Low doses are given initially (especially in patients who do not have hypertension), and the dose is gradually increased to the target level over a 4–8 week period (41).

CONCERNS: There are several potential complications with RAA suppression, including hypotension, worsening renal function, hyperkalemia, and angioedema. These drugs are contraindicated in patients with a history of angioedema from any cause. Also worthy of mention is that RAA suppression has shown no consistent benefit in patients with heart failure associated with preserved ejection fraction (HFpEF) (2).

Beta Blockers

Long-term treatment with beta blockers is recommended for all patients with HFrEF (2). The drugs that have proven effective in improving long-term outcomes include *carvedilol* and *sustained-release metoprolol (succinate)*, and the dosing regimens for these agents is shown in Table 18.5. *De novo* therapy is started at low doses and gradually advanced to target levels.

CONCERNS: Sudden withdrawal of beta blockers can result in a hyperadrenergic state known as "beta blocker rebound" (42). Therefore, for patients on long-term beta blocker therapy, treatment should be restarted as soon as the patient's condition has stabilized. Also worthy of mention is that the current guidelines for managing heart failure (2) includes no recommendation for beta blockers in heart failure associated with preserved ejection fraction.

SGLT2 Inhibitors

For unclear reasons, oral hypoglycemic therapy with sodium-glucose cotransporter 2 (SGLT2) inhibitors is associated with improved long-term outcomes in heart failure. This effect is independent of the glucose-lowering effect of the drugs, and occurs in both diabetic and nondiabetic patients (43). SGLT2 inhibitors are recommended for all patients with advanced heart failure (both HFrEF and HFpEF), regardless of the presence or absence of diabetes (2). The specific drugs and recommended doses are shown in Table 18.5.

CONCERNS: There is an increased risk of *euglycemic diabetic ketoacidosis* with SGLT2 inhibitors (44).

Aldosterone Antagonists

Aldosterone antagonists block sodium reabsorption in the renal collecting ducts, and can augment the diuretic effect of loop diuretics. These drugs (i.e., spironolactone, eplerenone) have shown a survival benefit in patients with HFrEF (2), and the recommended dosing regimens are shown in Table 18.5. As with all diuretics, these drugs should be used cautiously in cases of heart failure associated with a preserved ejection fraction, where the diastolic dysfunction can impair ventricular filling.

CONCERNS: Aldosterone antagonists can promote hyperkalemia, and should not be used in patients with renal failure (i.e., GFR <30 mL/min/1.73 m^2) or recent problems with hyperkalemia.

Positive Pressure Breathing

Positive intrathoracic pressures will reduce left ventricular afterload by decreasing the transmural wall pressure developed by the ventricle during systole. This promotes ventricular emptying by facilitating the inward movement of the ventricular wall during systole. As a result, positive pressure breathing can augment the stroke output of the left ventricle (see Figure 11.5).

Clinical studies have demonstrated that breathing with continuous positive airway pressure (CPAP) increases cardiac output in patients with left-sided heart failure (45), and hastens clinical improvement in patients with cardiogenic pulmonary edema (46,47). As a result of these observations, noninvasive positive-pressure breathing has become an accepted treatment

modality for acute heart failure associated with pulmonary edema.

A FINAL WORD

Be Cautious with Diuretics

The principle consequence in heart failure (other than cardiogenic shock) is venous congestion, hence the popular term “congestive heart failure”, and the popular use of diuretics. However, the following are reasons to avoid the overzealous use of diuretic therapy in patients with acute decompensated heart failure.

. The presence of acute, cardiogenic pulmonary edema is not always evidence of fluid overload, as the problem may be acute myocardial stiffening from cardiac ischemia, as seen in “flash pulmonary edema”.

. Intravenous furosemide causes a decrease in cardiac output in acute heart failure (31–33) via the dual effect of a drug-induced increase in left ventricular afterload (28) and a diuresis-induced decrease in ventricular preload.

. The tendency for diuresis to decrease cardiac output will be magnified in the 50% of cases of heart failure due to myocardial stiffening (i.e., heart failure with preserved ejection fraction), which impairs cardiac filling during diastole.

The above concerns might explain the observation that diuretic management in acute heart failure improves outcomes only when the diuretic dosing is limited (48).

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Chapter 19

Tachyarrhythmias

Variability is the law of life . . .

William Osler (*a*)

A rapid heart rate or *tachycardia* while at rest is evidence of a problem, but the tachycardia itself may not be the problem. This chapter describes tachycardias that *are* a problem (i.e., *tachyarrhythmias*), and require prompt evaluation and management. Many of the recommendations in this chapter are borrowed from the clinical practice guidelines listed in the bibliography at the end of the chapter (1–6).

RECOGNITION

The diagnostic evaluation of tachycardias (heart rate >100 beats/min) is based on 3 findings on the ECG: i.e., the duration of the QRS complex, the uniformity of the R-R intervals, and the characteristics of the atrial activity. This approach is outlined in the flow diagram in Figure 19.1. The duration of the QRS complex is used to distinguish *narrow-QRS-complex tachycardias* (QRS duration ≤0.12 sec) from *wide-QRS-complex tachycardias* (QRS duration >0.12 sec), which helps to identify the point of origin of the tachycardia, as described next.

Narrow-QRS-Complex Tachycardias

Tachycardias with a narrow QRS complex (≤0.12 sec) originate from a site above the AV conduction system, and are also known as *supraventricular tachycardias*. These include sinus tachycardia, atrial tachycardia, AV nodal re-entrant tachycardia (also called paroxysmal supraventricular tachycardia), atrial flutter, and atrial fibrillation. The specific arrhythmia can be identified using the uniformity of the R-R interval (i.e., the regularity of the rhythm), and the characteristics of the atrial activity, as described next.

Regular Rhythm

If the R-R intervals are uniform in length (indicating a regular rhythm), the possible arrhythmias include sinus tachycardia, AV nodal re-entrant tachycardia, and atrial flutter with a fixed (2:1, 3:1) AV block. The atrial activity on the ECG can identify each of these rhythms using the

following criteria:

. Uniform P waves and P–R intervals are evidence of sinus tachycardia.

. The absence of P waves suggests an AV nodal re-entrant tachycardia (see Figure 19.2).

. Sawtooth waves are evidence of atrial flutter.

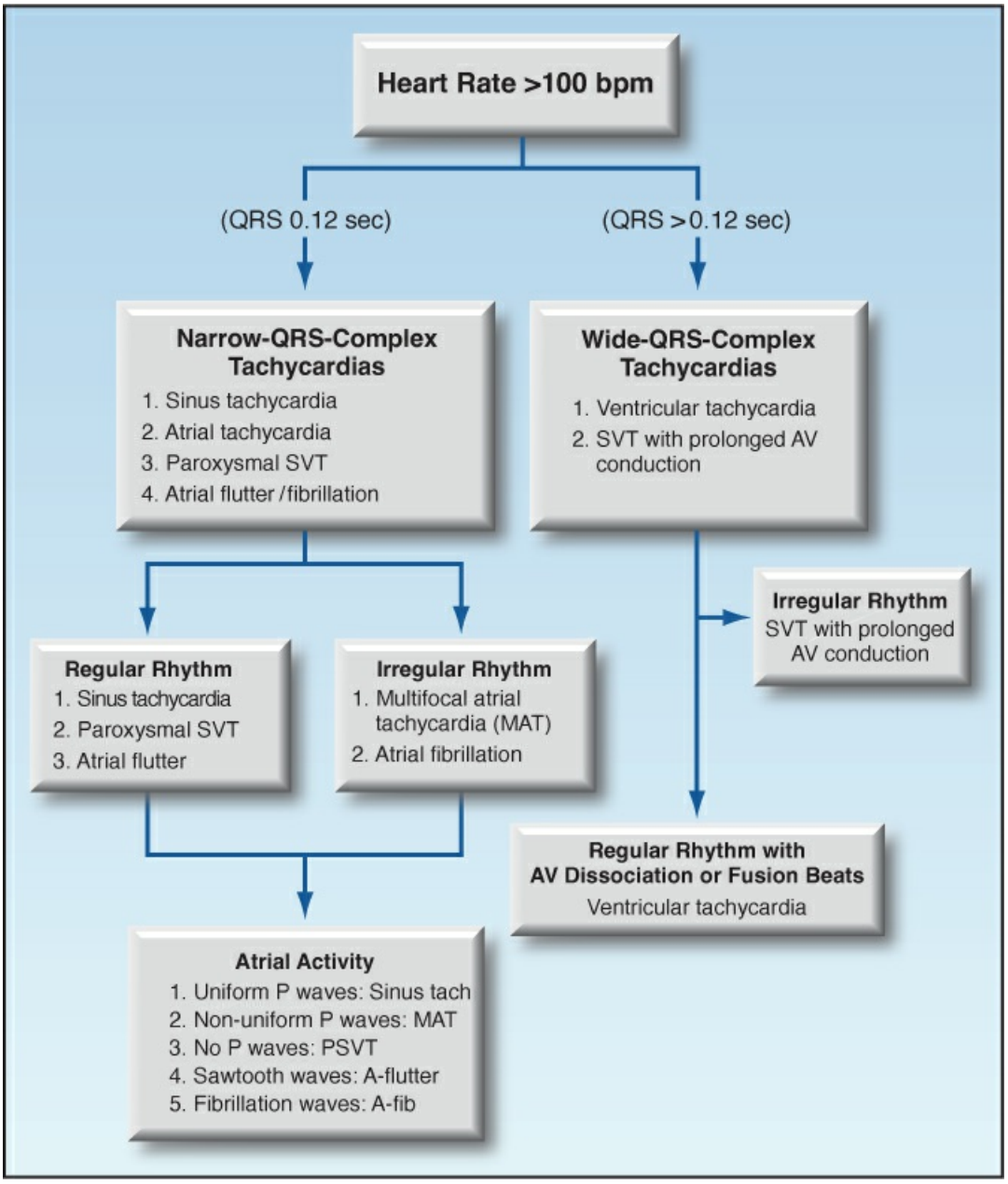

FIGURE 19.1 Flow diagram for the evaluation of tachycardias. See text for further details.

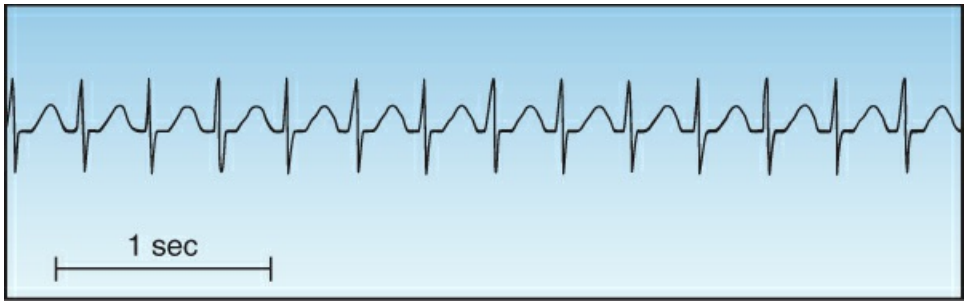

FIGURE 19.2 Narrow-QRS-complex tachycardia with a regular rhythm. Note the absence of visible P waves. This is an AV nodal re-entrant tachycardia, also known as a "paroxysmal supraventricular tachycardia" (paroxysmal SVT) because of its abrupt onset.

Irregular Rhythm

If the R-R intervals are not uniform in length (indicating an irregular rhythm), the most likely arrhythmias are multifocal atrial tachycardia and atrial fibrillation. Once again, the atrial activity on the ECG helps to identify each of these rhythms; i.e.,

. Multiple P wave morphologies and variable PR intervals are evidence of multifocal atrial tachycardia (see Panel A, Figure 19.3).

. The absence of P waves with highly disorganized atrial activity (fibrillation waves) is evidence of atrial fibrillation (see Panel B, Figure 19.3).

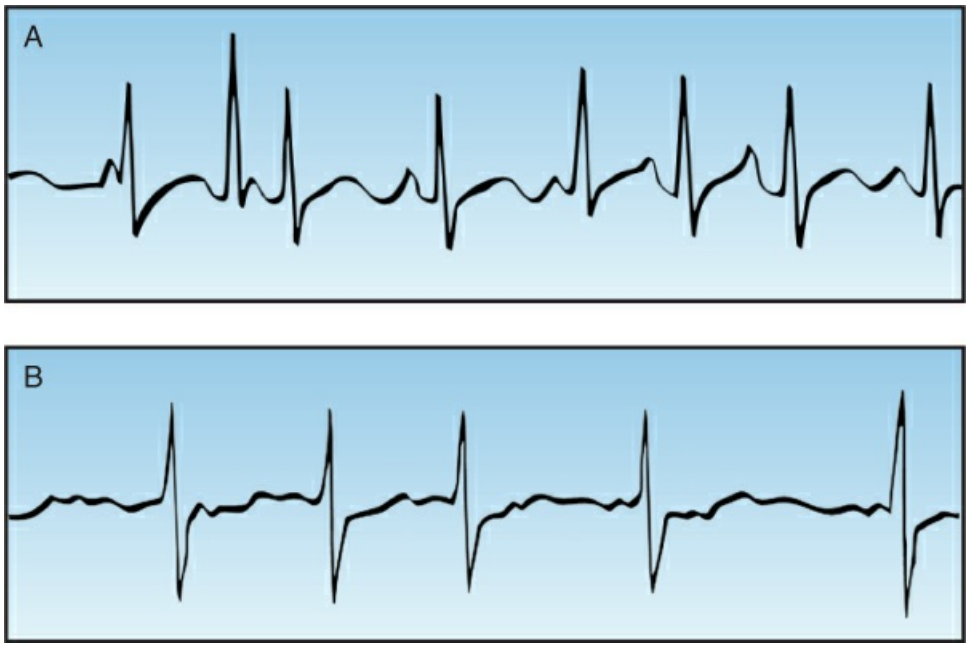

FIGURE 19.3 Narrow-QRS-complex tachycardias with an irregular rhythm. Panel A shows a multifocal atrial tachycardia (MAT), identified by multiple P wave morphologies and variable PR intervals. Panel B is atrial fibrillation, identified by the absence of P waves with highly disorganized atrial activity (fibrillation waves).

Wide- QRS- Complex Tachycardias

Tachycardias with a wide QRS complex (>0.12 sec) can originate from a site below the AV

conduction system (i.e., ventricular tachycardia), or they can represent a supraventricular tachycardia (SVT) with prolonged AV conduction (e.g., from a bundle branch block). These two arrhythmias can be difficult to distinguish. An irregular rhythm is evidence of an SVT with aberrant AV conduction, while certain ECG abnormalities (e.g., AV dissociation) provide evidence of VT. The distinction between VT and SVT with aberrant conduction is described in more detail later in the chapter.

ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults (prevalence = 2–4%), and is classified as paroxysmal (present ≤7 days), persistent (present for >7 days), long-standing persistent (present for >1 year), or permanent (when repeated attempts to restore sinus rhythm are unsuccessful) (3). Most patients are elderly (median age = 75 years) and have underlying cardiovascular or pulmonary disease (with the exception of hyperthyroidism). AF can also appear *de novo* in certain groups of hospitalized patients (see next).

Hospital-Related AF

New-onset AF is a reported risk in ICU patients, and in the postoperative period following major surgery.

ICU-Related AF

The reported incidence of ICU-related AF varies widely (from 2% to 44%), and is more likely to appear in elderly patients with coronary disease, sepsis, shock, or respiratory failure (7,8). The AF resolves spontaneously in up to 25% of cases (7), but it tends to recur, and rehospitalization for AF is reported in 20% of cases (8). Stroke is a risk, but the reported incidence is only 1% in the ensuing 3 years (8).

Postoperative AF

Postoperative AF is reported in up to 45% of cases involving cardiac and non-cardiac thoracic surgery, and up to 10% of cases involving other major surgeries (7,9). It usually appears in the first 5 postoperative days (9), and follows the same course as ICU-related AF. Prophylaxis with β-blockers and magnesium has been effective in the AF that follows cardiac surgery AF (10).

Adverse Consequences

AF can impair cardiac performance and increase the risk of thromboembolic stroke.

Cardiac Performance

Atrial contraction is responsible for about 25% of the ventricular end diastolic volume (11). Loss of this atrial contribution (from AF) has little noticeable effect unless diastolic filling is already impaired by mitral stenosis or reduced ventricular compliance (e.g., from ventricular hypertrophy). Under these conditions, a rapid heart rate can decrease cardiac stroke output (because of the decreased time for ventricular filling).

The influence of ventricular filling time in AF is illustrated by the arterial pressure

waveforms in Figure 19.4. Note that close spacing between two heart beats (which shortens the time for ventricular filling), results in a decrease in systolic pressure (which is a reflection of the stroke volume). This effect can result in a "pulse deficit" (i.e., a decrease in the peripheral pulse rate relative to the apical impulses), indicating that the stroke output of the heart is not always reaching the periphery. Although rarely mentioned, monitoring the pulse deficit could be useful for identifying the end-point of rate control in AF (12).

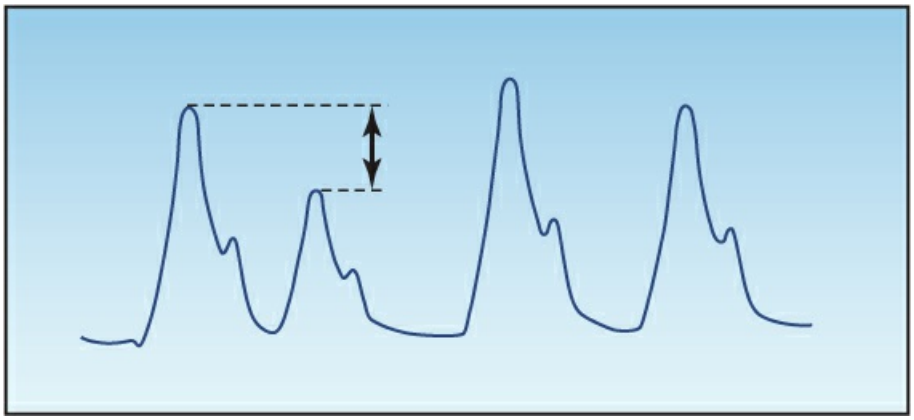

FIGURE 19.4 Arterial pressure tracings in AF. Note that there is a decrease in systolic pressure when two heart beats occur in rapid succession. This effect can produce a "pulse deficit", where apical impulses are not always transmitted to the periphery.

Stroke

Atrial fibrillation predisposes to thrombus formation in the left atrium, especially in the left atrial appendage, and these thrombi can dislodge and embolize in the cerebral circulation to produce an acute ischemic stroke. Overall, AF increases the risk of stroke 5-fold (3–5), but the risk is not homogeneous, and is influenced by the presence of certain risk factors (which are described later). The increased risk of stroke pertains to all types of AF, except first episodes of AF that are <48 hrs in duration. Recommendations for stroke-prevention with antithrombotic therapy are presented later.

Heart Rate Control

In patients with rapid AF who are hemodynamically stable, the initial goal is to slow the heart rate with drugs that prolong AV conduction. A variety of drugs are available for this purpose (13), and the popular ones are included in Table 19.1. The following is a brief description of each drug. (*Caveat:* These drugs should not be used if the AF originates from an accessory pathway in the AV node, as described later).

TABLE 19.1 Drug Regimens for Acute Rate Control in Atrial Fibrillation

Drug	Dosing Regimens and Comments
Diltiazem	Dosing: 0.25 mg/kg IV over 2 min, then infuse at 5–15 mg/hr. Comment: A popular agent for acute rate control, but use is limited by the risk of hypotension (20–30% of cases), and by negative inotropic effects.

Amiodarone	Dosing: 150 mg IV over 10 min, and repeat if needed, then infuse at 1 mg/min for 6 hr and 0.5 mg/min for 18 hr. Total dose should not exceed 2.2 grams in 24 hrs. Comment: An effective alternative to diltiazem and beta blockers, and may be preferred in HFrEF. Can occasionally promote conversion to sinus rhythm.
Metoprolol	Dosing: 2.5–5 mg IV over 2 min, and repeat every 5–10 min if needed to a total of 3 doses. Comment: Most effective in AF associated with hyperadrenergic states. Similar to diltiazem in risk of hypotension and negative inotropic effects.
Esmolol	Dosing: 500 µg/kg IV bolus, then infuse at 50 µg/kg/min. Increase dose in increments of 25 µg/kg/min every 5 min if needed to a maximum rate of 200 µg/kg/min. Comment: An ultra-short-acting β blocker that permits rapid dose titration. Other features similar to metoprolol.
Digoxin	Dosing: 0.25 mg IV every 2 hrs to a total dose of 1.5 mg, then 0.125–0.375 mg IV daily. Comment: Slow-acting drug that should not be used alone for acute rate control. Used primarily for long-term rate control in patients with HFrEF.

See text for references. HFrEF = heart failure with reduced ejection fraction.

Diltiazem

The most popular agent for acute rate control in AF is the calcium channel blocker diltiazem, which is given as an intravenous bolus followed by a continuous infusion. The bolus dose produces effective rate control within one hour in 55% of patients (14), and the continuous infusion maintains rate control in up to 90% of cases (15). The graph in Figure 19.5 shows that diltiazem is more effective than either amiodarone or digoxin in the first few hours of drug therapy (16).

COMPLICATIONS: The use of diltiazem is limited by the risk of hypotension, which is reported in about 20–30% of cases (15,17). Diltiazem also has negative inotropic effects, which limits its use in patients with heart failure associated with reduced ejection fraction.

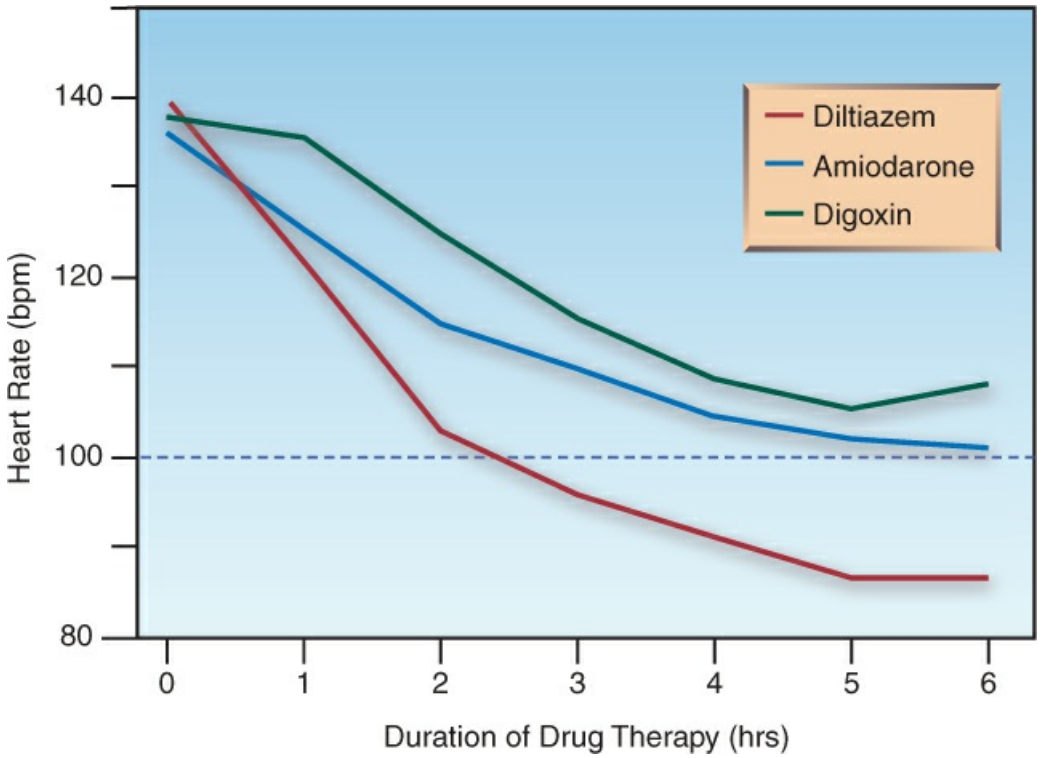

FIGURE 19.5 Comparison of acute rate control with intravenous diltiazem, amiodarone, and digoxin in patients with uncomplicated atrial fibrillation. Data from Reference 16.

β-Receptor Antagonists

β-blockers achieve successful rate control in 70% of cases of rapid AF (18), and are most effective in hyperadrenergic states. Two β-blockers with proven efficacy in acute rate control are *esmolol* (Brevibloc) and *metoprolol* (Lopressor), and their dosing regimens are shown in Table 19.1. Both are cardioselective agents that preferentially block β-1 receptors in the heart, but both are limited by the risk of hypotension. Esmolol is more appealing than metoprolol because it is an ultra short-acting drug (serum half-life is only 9 minutes), which allows rapid dose titration (19).

Amiodarone

Amiodarone is an effective alternative to diltiazem or beta blockers in patients who are resistant or intolerant to these drugs (20). It also produces less cardiac depression than diltiazem or beta blockers, and is favored in some guidelines for patients with heart failure and reduced ejection fraction (4). Amiodarone is also an antiarrhythmic agent (Class III), and is capable of converting AF to a sinus rhythm. However, the success rate for cardioversion is variable, and some studies show no difference in the rate of cardioversion with amiodarone and diltiazem (17).

COMPLICATIONS: Intravenous amiodarone does not have the feared side effects associated with long-term therapy (e.g., pulmonary fibrosis, thyroid dysfunction). Hypotension can occur, but the incidence is far lower than with diltiazem (17). The hypotensive effect can be attributed to a solvent (polysorbate 80 surfactant) used to enhance the water solubility of amiodarone, since the aqueous formulation of amiodarone does not cause hypotension (21). Amiodarone can also

prolong the QT interval, and “torsade de pointes” has been reported, although rarely (22). Finally, amiodarone has several drug interactions by virtue of its metabolism by the cytochrome P450 enzyme system in the liver. The most relevant interactions in the ICU setting are inhibition of digoxin and warfarin metabolism.

TRANSITION TO ORAL THERAPY: Transition from IV to oral amiodarone begins with an oral dose of 400 mg, which is given 4–5 hours before discontinuing the infusion. The initial oral regimen is 400 mg twice daily, which is continued until the total loading dose (IV and PO) reaches 10 grams (22). (The initial 24-hour IV regimen is a total dose of about one gram.) Thereafter, the daily dose can be reduced to the usual maintenance dose (100–200 mg once daily).

Digoxin

Digoxin prolongs conduction in the AV node, and is used for long-term rate control in patients with AF and heart failure with reduced ejection fraction. However, its value for acute rate control is limited because *the response to intravenous digoxin is slow to develop*. This is demonstrated in Figure 19.5 (16). Note that there is little effect in the first hour after drug administration, and the heart rate has not reached the desired end-point (<100 bpm) after 6 hours. Because of this delayed response, intravenous digoxin should not be used alone for acute rate control in AF (3,13). It can, however, be used as an adjunct to diltiazem or beta blockers in patients with heart failure or labile BP.

End-Point of Rate Control

There is a surprising lack of agreement about the end-point of rate reduction in AF, and heart rates of 80 bpm to 110 bpm have been used as end-points in individual studies (3). However the phenomenon shown in Figure 19.4 suggests another approach to this issue; i.e., *elimination of the pulse deficit, or resolution of the variable systolic pressure in rapid AF, provides a more physiological goal of heart rate reduction in AF*. This approach is often overlooked, but deserves your consideration.

Electrical Cardioversion

Synchronized, direct-current cardioversion is reserved for hemodynamically unstable patients. Biphasic shocks have a greater success rate and require lower energy levels than monophasic shocks (23). An energy level of 100 joules is usually successful with biphasic shocks (vs. 200 joules for monophasic shocks) (23). Fixed-energy attempts are considered more effective than an escalating energy approach (3). The success rate of cardioversion is greatest for new-onset or recent-onset AF.

Cardiac ultrasound (via the transesophageal approach, if time permits) is required prior to cardioversion to determine the presence or absence of atrial thrombi. Anticoagulation with a direct-acting oral agent is started as soon as possible (prior to, or immediately after the procedure) in appropriate candidates. Anticoagulation is not required for new-onset AF that is less than 48 hours in duration.

Stroke Prevention

As mentioned earlier, there is an increased risk of thromboembolic stroke in AF, but a number of

factors influence this risk (as well as the need for anticoagulant prophylaxis).

Risk Assessment

The decision to use anticoagulant therapy in AF is based on a scoring system that is shown in Table 19.2. There are 10 identified risk factors for stroke, with the highest risk being advanced age (>75 years), and a prior history of stroke, transient ischemic attack (TIA) or venous thromboembolism (VTE). Patients who are definite candidates for anticoagulation are considered to have at least a five-fold higher risk of stroke (or a yearly incidence >5%). It is important to mention that the risk assessment in Table 19.2 does not apply to valvular AF (i.e., AF associated with mitral stenosis or a prosthetic valve), which always requires anticoagulation (3).

Contraindications to anticoagulation in AF include active hemorrhage, a history of intracerebral hemorrhage, intracranial tumor, recurrent bleeding from a lesion that is still present, and a platelet count <50,000/μL (3,4). Of interest, *a history of falls is not a contraindication to anticoagulant therapy* (24).

TABLE 19.2 Risk Assessment for Oral Anticoagulation in Atrial Fibrillation

CHA_2DS_2-VASc Scoring		Indications for Anticoagulation
Condition	**Points**	
(C) CHF	1	**Definite** Males: ≥2 points Females: ≥3 points
(H) Hypertension	1	
(A) Age >75 yrs	2	
(D) Diabetes	1	
(S) Stroke/TIA/VTE	2	**Consider** Males: 1 point Females: 2 points
(V) Vascular Disease	1	
(A) Age 65–74 yrs	1	
(Sc) Sex Category (♀)	1	

VTE = venous thromboembolism. From References 3–5.

Oral Anticoagulants

The oral anticoagulants used for stroke prevention in AF are shown in Table 19.3.

Warfarin:

Warfarin is the first oral anticoagulant approved for clinical use (in the 1950s), and acts indirectly by inhibiting the synthesis of vitamin K-dependent clotting factors (Factors II, VII, IX, and X). Anticoagulation with warfarin reduces the incidence of stroke (by as much as 65%) in both valvular and nonvalvular AF (3–5,13,25). However, warfarin has a narrow therapeutic window (i.e., the difference between therapeutic and toxic drug levels), which increases the likelihood of both inadequate and excessive anticoagulation, and requires routine monitoring of hemostasis (with the international normalized ratio, or INR).

TABLE 19.3	Oral Anticoagulants for Atrial Fibrillation
Drug	**Dosing Recomendations**
Dabigatran (Pradaxa)	Standard Dose: 50 mg BID. Reduced Dose: 110 mg BID for age ≥80 yrs or CrCL <30 mL/min.
Rivaroxaban (Xarelto)	Standard Dose: 20 mg once daily. Reduced Dose: 15 mg once daily for CrCL <30 mL/min.
Apixaban (Eliquis)	Standard Dose: 5 mg BID. Reduced Dose: 2.5 mg BID for 2 of the following: age ≥80 yrs, weight ≤60 kg, serum creatinine ≥1.5 mg/dL.
Edoxaban	Standard Dose: 60 mg once daily. Reduced Dose: 30 mg once daily for CrCL <30 mL/min, weight ≤60 kg, or therapy with erythromycin or ketoconazole.
Warfarin (Coumadin)	Starting dose is usually 5 mg once daily, which is adjusted to achieve an INR of 2–3.

From the clinical practice guidelines in Reference 3. CrCL =-creatinine clearance (estimated).

Direct-Acting Oral Anticoagulants

The direct-acting oral anticoagulants (DOACs), which include direct thrombin inhibitors (e.g., dabigatran) and drugs that inhibit Factor Xa (e.g., rivaroxaban, apixaban, and edoxaban), have a more predictable anticoagulant effect than warfarin, and are given in fixed doses, without monitoring any tests of hemostasis. Clinical studies in patients with nonvalvular AF have shown that DOACs are as effective as warfarin in reducing the incidence of stroke, and have a lower incidence of major bleeding (26–29). Based on these observations, *DOACs are preferred to warfarin for stroke reduction in patients with nonvalvular AF* (3–5). Each DOAC is considered equivalent to the others, but edoxaban may be less effective for stroke reduction (29), and dabigatran may have a greater risk of bleeding (26).

The preference for DOACs does not extend to valvular AF (i.e., AF associated with significant mitral stenosis or the presence of any prosthetic valve). In this situation, warfarin is considered superior to DOACs for stroke prevention (3–5).

DOSING: The recommended dosing for each DOAC is shown in Table 19.3. Note that a dose reduction is required for all DOACs in patients with renal insufficiency (creatinine clearance <30 mL/min). In this situation, Factor Xa levels can be measured to assess the adequacy of anticoagulation. The consensus opinion is that DOACs should be avoided in patients with end-stage renal failure (creatinine clearance <15 mL/min) (3–5).

Wolff-Parkinson-White Syndrome

The Wolff-Parkinson-White (WPW) syndrome (short P–R interval and delta waves before the QRS) is characterized by recurrent supraventricular tachycardias that originate from an accessory pathway in the AV node. (The mechanism for these tachycardias is explained in the section on re-entrant tachycardias.) When atrial fibrillation occurs in a patient with an accessory pathway,

drugs that block conduction in the AV node, (e.g., calcium channel blockers, β-blockers, digoxin) are unlikely to slow the ventricular rate because the accessory pathway is not blocked. Furthermore, selective block of the AV node can precipitate ventricular fibrillation (6). Therefore, *drugs that block the AV node should NOT be used when AF is associated with the WPW syndrome*. The preferred management in this situation is electrical cardioversion, or pharmacological cardioversion with amiodarone or procainamide.

MULTIFOCAL ATRIAL TACHYCARDIA

Multifocal atrial tachycardia or MAT (see Panel A in Figure 19.3) is a disorder of the elderly (average age = 70), and over half of the cases occur in patients with chronic lung disease (30). Other associated conditions include magnesium and potassium depletion, and coronary artery disease (31).

Acute Management

The following measures are recommended for the acute management of MAT, but this is a stubborn arrhythmia that is often refractory to medical management.

. Correct hypomagnesemia and hypokalemia if necessary. If both electrolyte abnormalities co-exist, the magnesium deficiency must be corrected before potassium deficits can be replaced. This is explained in Chapter 37.

. Since serum magnesium levels can be normal when total body magnesium is depleted (also explained in Chapter 37), intravenous magnesium can be given empirically using the following regimen: *Start with 2 grams $MgSO_4$ (in 50 mL saline) IV over 15 minutes, then infuse 6 grams $MgSO_4$ (in 500 mL saline) over 6 hours*. This regimen had a remarkable 88% success rate in converting MAT to a sinus rhythm in one study (31), and the effect was independent of serum magnesium level.

. If the prior measures fail, and COPD is not the cause of the MAT, *metoprolol in the doses shown in Table 19.1 has a reported 80% success rate in converting MAT to sinus rhythm* (30).

. If metoprolol is a concern in patients with COPD, the calcium channel blocker *verapamil* can be effective. Verapamil converts MAT to sinus rhythm in less than 50% of cases (30), but it can slow the ventricular rate. *The dose is 0.25–5 mg IV over 2 min, which can be repeated every 15–30 min, if necessary, to a total dose of 20 mg* (32). Verapamil is a potent negative inotropic agent, and is not recommended for patients with heart failure and a reduced ejection fraction (32).

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIAS

Paroxysmal supraventricular tachycardias (PSVT) are narrow-QRS-complex tachycardias that are second only to atrial fibrillation as the most prevalent rhythm disturbances in the general population.

Mechanism

These arrhythmias occur when impulse transmission in one pathway of the AV conduction system is slowed. This creates a difference in the refractory period for impulse transmission in the abnormal and normal conduction pathways, and this allows impulses travelling down one pathway to travel back through the other pathway. The retrograde transmission of impulses is called *re-entry*, and it results in a circular pattern of impulse transmission that is self-sustaining; i.e., a *re-entrant tachycardia*. Re-entry is triggered by an ectopic atrial impulse in one of the two conduction pathways, which results in the abrupt onset that is characteristic of re-entrant tachycardias.

There are 5 different types of PSVT, based on the location of the re-entrant pathway. The most common PSVT is *AV nodal re-entrant tachycardia*, where the re-entrant pathway is located in the AV node.

AV Nodal Re-Entrant Tachycardia

AV nodal re-entrant tachycardia (AVNRT) accounts for 50 to 60% of cases of PSVT (33). It typically appears in patients who have no history of heart disease, and is more common in women than men. The onset is abrupt, and the predominant complaints are palpitations and lightheadedness. There is no evidence of heart failure or myocardial ischemia, and significant hemodynamic compromise is uncommon. The ECG shows a narrow- QRS-complex tachycardia with a regular rhythm and a heart rate between 140 and 250 bpm (33). There are often no visible P waves on the ECG, as shown in Figure 19.2.

Because AVNRT has a regular rhythm, it is often mistaken for sinus tachycardia. However, the onset is abrupt in AVNRT and gradual in sinus tachycardia, while the ECG shows no visible P waves in AVNRT, but there are P waves before each QRS complex in sinus tachycardia. A 12-lead ECG is often necessary for identifying P waves (which are usually most prominent in the anterior precordial leads and inferior limb leads).

Vagal Maneuvers

Maneuvers that increase vagal tone are recommended as an initial attempt to terminate AVNRT (34). A variety of maneuvers have been identified (34), including (with the patient in the supine position) carotid sinus massage (only when there are no carotid bruits), the Valsalva maneuver (maximal expiratory effort with a closed glottis), the Mueller maneuver (maximal inspiratory effort with a closed glottis), induced gag reflex (by stimulating the posterior oropharynx with a tongue depressor), and application of an ice-cold, wet towel to the face (in an attempt to elicit a diving reflex).

Vagal maneuvers have had limited success in terminating AVNRTs. In one prospective study, the conventional Valsalva maneuver and carotid sinus massage had success rates of 24% and 9%, respectively (35). However in the same study, a modified Valsalva maneuver (performed by elevating the patients legs after the standard Valsalva maneuver) had a success rate of 44% (35).

Adenosine

When vagal maneuvers are ineffective, *adenosine is the drug of choice for terminating AVNRT* (34). Adenosine is an endogenous nucleotide that relaxes vascular smooth muscle and slows

conduction in the AV node. When given by rapid intravenous injection, adenosine has a rapid onset of action (<30 sec) and produces a transient AV block that can terminate AV nodal re-entrant tachycardias. Adenosine is quickly cleared from the bloodstream (by receptors on RBCs and endothelial cells), and the effects last only 1–2 minutes.

TABLE 19.4 Intravenous Adenosine for Paroxysmal SVT

Feature	Recommendations
Dosing Regimen	1. Deliver through a peripheral vein. 2. Give 6 mg by rapid IV injection and flush catheter with saline. 3. If response inadequate after 2 min, give 12 mg by rapid IV injection and flush catheter with saline. 4. If response still inadequate after 2 min, another 12 mg can be given by rapid IV injection.
Dose Adjustments	Decrease dose by 50% for: • Drug delivery into the superior vena cava • Patient receiving calcium channel blocker, β-blocker, or dipyridamole.
Drug Interactions	• Dipyridamole (blocks adenosine uptake) • Theophylline (blocks adenosine receptors)
Adverse Effects	• Bradycardia, AV Block (50%) • Facial flushing (20%) • Dyspnea (12%) • Chest Pressure (7%)
Contraindications	• Asthma • 2nd or 3rd^0 AV block • Sick sinus syndrome

From References 34,36, and 37.

Dosing Considerations

The dosing regimen for adenosine is shown in Table 19.4 (34,36,37). The initial dose is 6 mg, which is injected rapidly into a peripheral vein and followed by a saline flush. Optimal results are obtained if the drug is injected at the hub of the catheter. If conversion to sinus rhythm does not occur after 2 minutes, a second 12 mg dose is given, and this can be repeated once if necessary. This regimen *terminates re-entrant tachycardias in over 90% of cases* (34).

The effective dose of adenosine for terminating AVNRT was determined in studies that used drug injection into peripheral veins. However, ventricular asystole has been reported when standard doses of adenosine are given through central venous catheters (38), so *a dose reduction of 50% has been recommended* by some (including the manufacturer) *when adenosine is delivered through a central venous catheter* (38).

Adverse Effects

The adverse effects of adenosine are short-lived. The most frequent adverse effect is post-conversion bradycardia, including various degrees of AV block. The AV block is refractory to atropine, but resolves spontaneously within 60 seconds (37). Dipyridamole enhances the AV

block produced by adenosine, and the two drugs should not be used together (37). Adenosine is contraindicated in patients with asthma; i.e., there is evidence that adenosine produces a sense of dyspnea, but not bronchospasm, in asthmatic subjects (39).

Other Therapies

When PSVT does not respond to adenosine, the calcium channel blockers diltiazem or verapamil can be effective. (The dosing regimen for diltiazem is shown in Table 19.1, and the dosing regimen for verapamil is presented in the section on multifocal atrial tachycardia). For the rare case of PSVT that is resistant to drugs or is hemodynamically unstable, synchronized electrical cardioversion will terminate the rhythm, but energy levels greater than 100 J may be necessary (34).

VENTRICULAR TACHYCARDIA

Ventricular tachycardia (VT) is a wide-QRS-complex tachycardia that has an abrupt onset, a regular rhythm, and a rate that is typically 140–200 bpm. The appearance can be *monomorphic* (uniform QRS complexes) or *polymorphic* (multiple QRS morphologies). VT rarely occurs in the absence of structural heart disease (2), and when it is sustained (i.e., lasts longer than 30 seconds), it can be an immediate threat to life.

VT versus SVT

Monomorphic VT can be difficult to distinguish from an SVT with prolonged AV conduction. This is demonstrated in Figure 19.6. The tracing in the upper panel shows a wide-QRS-complex tachycardia that looks like monomorphic VT. The tracing in the lower panel shows spontaneous conversion to sinus rhythm. Note that the QRS complex remains unchanged after the arrhythmia is terminated, revealing an underlying bundle branch block. Thus, the apparent VT in the upper panel is actually an SVT with a pre-existing bundle branch block.

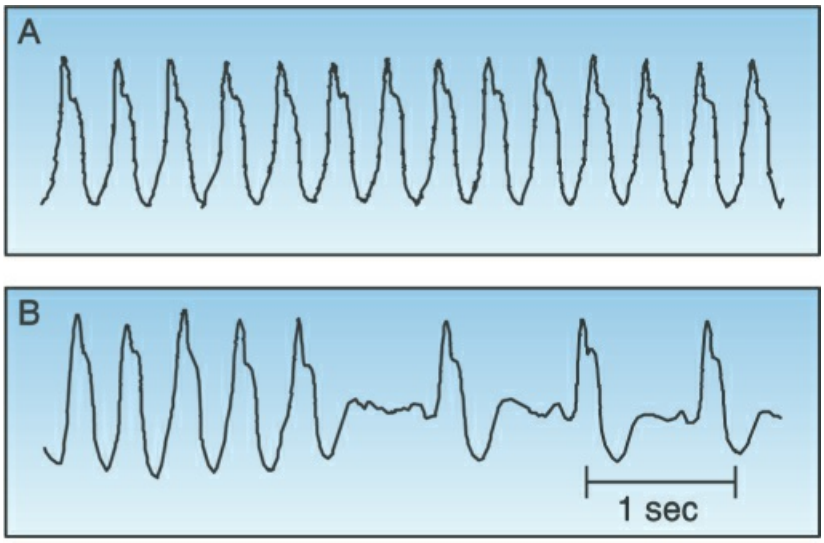

FIGURE 19.6 Upper panel shows a wide-QRS-complex tachycardia that looks like monomorphic VT. However, the lower panel shows spontaneous conversion to a sinus rhythm,

which reveals an underlying bundle branch block, indicating that the rhythm in the upper panel is an SVT with a pre-existing bundle branch block. Tracings courtesy of Dr. Richard M. Greenberg, MD.

Clues

There are two abnormalities on an ECG that will identify VT as the cause of a wide-QRS-complex tachycardia.

. The atria and ventricles beat independently in VT, and this results in *AV dissociation* on the ECG, where there is no fixed relationship between P waves and QRS complexes. (P waves are most visible in the inferior limb leads and the anterior precordial leads.)

. The presence of fusion beats like the one in Figure 19.7 is indirect evidence of VT. A fusion beat is produced by the retrograde transmission of a ventricular ectopic impulse that collides with a supraventricular (e.g., sinus node) impulse. The result is a hybrid QRS complex that is a mixture of the normal QRS complex and the ventricular ectopic impulse. The presence of a fusion beat (which should be evident on a single-lead ECG tracing) is thus indirect evidence of ventricular ectopic activity.

If there is no definitive evidence of VT on the ECG, the presence or absence of heart disease can be useful; i.e., *VT is the cause of 95% of wide-QRS-complex tachycardias in patients with underlying heart disease* (40). Therefore, a wide-QRS-complex tachycardia should be treated as probable VT in any patient with underlying heart disease.

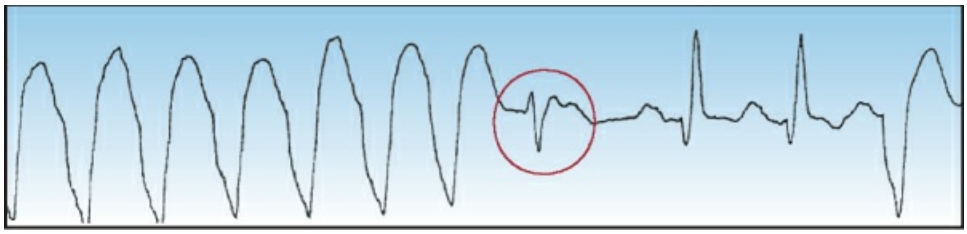

FIGURE 19.7 An example of a fusion beat (circled in red), which is a hybrid QRS complex produced by the collision of a ventricular ectopic impulse and a supraventricular (e.g., sinus node) impulse. The presence of fusion beats is evidence of ventricular ectopic activity.

Management

The management of patients with a wide-QRS-complex tachycardia can be organized as shown in Figure 19.8.

. If there is evidence of hemodynamic compromise, *electrical cardioversion* is the appropriate intervention, regardless of whether the rhythm is VT or SVT with aberrant conduction. The shocks should be synchronized (timed with the QRS complex) and a low-energy shock of 100 J (biphasic or monophasic shocks) should terminate most cases of monomorphic VT (41). If this is unsuccessful, try 100 J again but use biphasic shocks. You can escalate to 200 J, but avoid higher energy shocks (e.g., 360 J) because they damage the myocardium (41).

. If there is no evidence of hemodynamic compromise and the diagnosis of VT is certain, intravenous amiodarone should be used to terminate the arrhythmia. *Amiodarone is the favored drug for suppressing monomorphic VT* (4), and the dosing regimen is shown in Figure 19.8.

. If there is no evidence of hemodynamic compromise and the diagnosis of VT is uncertain, the response to adenosine can be helpful because adenosine will abruptly terminate most cases of paroxysmal SVT, but will not terminate VT. If a wide-QRS-complex tachycardia is refractory to adenosine, the likely diagnosis is VT, and intravenous amiodarone is indicated for arrhythmia suppression.

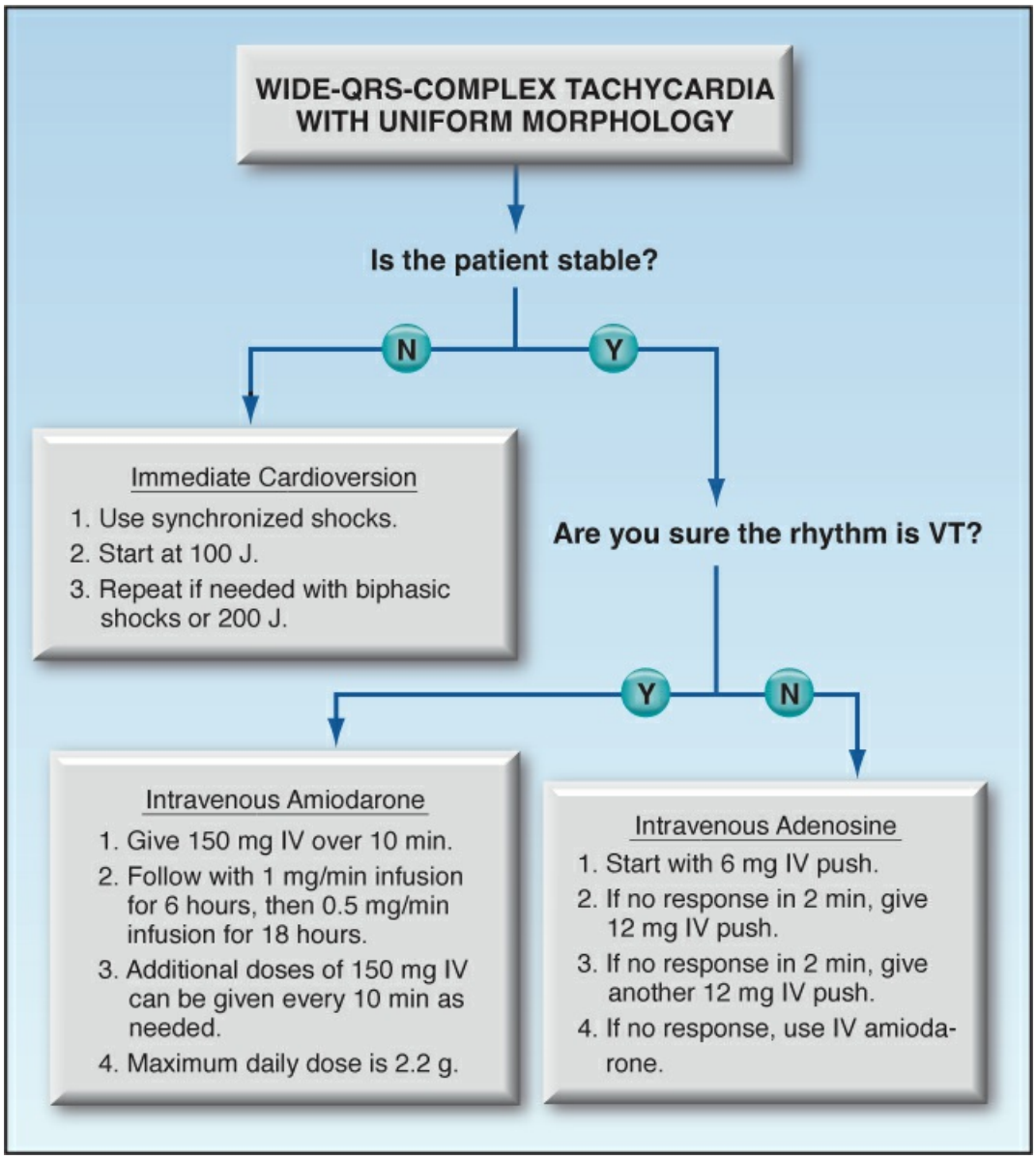

FIGURE 19.8 Flow diagram for the acute management of patients with wide-QRS-complex tachycardia. Based on recommendations in Reference 4.

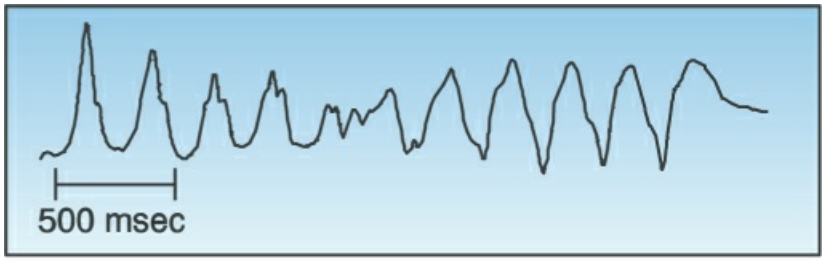

FIGURE 19.9 Torsade de pointes, a polymorphic ventricular tachycardia described as “twisting around the (isoelectric) points”. Tracing courtesy of Dr. Richard M. Greenberg, MD.

Torsade de Pointes

Torsade de pointes ("twisting around the points") is a polymorphic VT with QRS complexes that appear to be twisting around the isoelectric line of the ECG, as shown in Figure 19.9. This arrhythmia is usually associated with a prolonged QT interval, and it can be congenital or acquired. The acquired form is much more prevalent, and is caused by a variety of drugs and electrolyte abnormalities that prolong the QT interval (42,43). There is also a polymorphic VT that is associated with a normal QT interval, and the predisposing condition in this case is myocardial ischemia (42).

Predisposing Factors

The drugs most frequently implicated in torsade de pointes are listed in Table 19.5 (43). The prominent offenders are antiarrhythmic agents (Class IA and III), macrolide antibiotics, neuroleptic agents (phenothiazines and butyrophenones), and cisapride (a pro-motility drug). The electrolyte disorders that prolong the QT interval include hypokalemia, hypocalcemia, and hypomagnesemia.

TABLE 19.5 Drugs That Can Induce Torsade de Pointes

Antiarrhythmics	Antimicrobials	Neuroleptics	Others
IA: Quinidine, Disopyramide, Procainamide	Clarithromycin	Chlorpromazine	Cisapride
III: Ibutilide, Sotalol	Erythromycin	Tioridazine	Methadone
	Pentamidine	Droperidol	
		Haloperidol	

From Reference 43. For a complete list of drugs, go to www.torsades.org

Measuring the QT Interval

The QT interval is the ECG manifestation of ventricular depolarization and repolarization, and is measured from the onset of the QRS complex to the end of the T wave. The longest QT intervals are usually in precordial leads V3 and V4, and these leads are most reliable for assessing QT prolongation. The QT interval varies inversely with heart rate, and a rate-corrected QT interval (QTc) provides a more accurate assessment of QT prolongation. The accepted method for

determining the QTc is to divide the QT interval by the square root of the R-R interval (43–45); i.e.,

$$QTc = QT/\sqrt{R\text{-}R} \quad (19.1)$$

A normal QTc is ≤0.44 seconds, and a QTc >0.5 seconds represents a risk for torsade de pointes (45). However, the importance of QT prolongation as a risk factor for torsade de pointes is not as advertised, because prolonged QT intervals are commonplace in ICU patients, while torsade de pointes is an uncommon arrhythmia.

Management

The management of polymorphic VT can be summarized as follows:

. Sustained polymorphic VT requires nonsynchronized electrical cardioversion (i.e., defibrillation) (42).

. Intravenous magnesium is popular for terminating torsade de pointes, and can be combined with electrical cardioversion (46). There is no consensus about the magnesium dose in this setting, but the current ACLS guidelines recommend 1–2 grams of magnesium sulfate ($MgSO_4$) IV over 15 minutes (6).

. Other measures aimed at preventing recurrences of torsade de pointes include correcting hypokalemia and hypomagnesemia (high-risk electrolyte abnormalities) and discontinuing high-risk drugs (e.g., haloperidol).

. For polymorphic VT with a normal QT interval, amiodarone or β-blockers can help to prevent recurrences (47).

A FINAL WORD

Managing the Muddle

The first glance at the variety of cardiac arrhythmias and treatment options is often a befuddling experience, and the following tips can help to unravel things.

For a narrow-complex tachycardia:

. If the rhythm is regular, the candidates are sinus tachycardia, paroxysmal supraventricular tachycardia (PSVT), or atrial flutter. However, PSVT is uncommon in ICU patients (and usually occurs in younger patients with no structural heart disease).

. If the rhythm is highly irregular, it is most likely atrial fibrillation. Another candidate is multifocal atrial tachycardia (MAT), which is seen in patients with chronic lung disease.

. Be aware that rapid atrial fibrillation can appear to be a regular rhythm.

For a wide-complex tachycardia:

. If the rhythm is irregular, it is likely to be atrial fibrillation (or MAT) with prolonged AV

conduction. Ventricular tachycardia is never irregular.

. If the rhythm is regular, it is most likely ventricular tachycardia. However, rapid atrial fibrillation with prolonged AV conduction can also appear to be regular.

. If the height of the complexes is increasing and decreasing, the rhythm is likely to be “torsade de pointes”.

Finally, atrial fibrillation is (by far) the most common arrhythmia you will encounter in the ICU, so focus your attention accordingly.

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Chapter 20

Acute Coronary Syndromes

The study of the causes of things must be preceded by the study of things caused.

John Hughlings Jackson (1835–1911)

One of the seminal moments in cardiac critical care was the discovery (in 1980) that transmural myocardial infarction (MI) was the result of an occlusive thrombus in a coronary artery. This led to the introduction of thrombolytic therapy (in the mid-1980s), followed by the superseding technology of balloon angioplasty and stent placement. Advances in reperfusion therapy have improved outcomes, and have contributed to 20% decline in the annual mortality rate from coronary disease over the past decade (from 2010 to 2020) (1). However, coronary artery disease continues to be the leading cause of death in the United States (1), so there is more work to be done.

This chapter describes the diagnosis and early management of acute myocardial infarction and unstable angina (the *acute coronary syndromes*), with an emphasis on management in the first 24–36 hours after presentation. Also included is a section on acute aortic dissection, which has a clinical presentation that can be confused with acute coronary syndromes. Many of the recommendations in this chapter are derived from the clinical practice guidelines listed in the bibliography at the end of the chapter (2–7).

CORONARY THROMBOSIS

Pathogenesis

As just mentioned, acute myocardial infarction is the result of an occlusive thrombus in one or more coronary arteries. The trigger for thrombus formation is rupture of an atherosclerotic plaque, which releases thrombogenic lipids (see Figure 20.1). Plaque disruption is attributed to inflammation (8), but hydraulic shear stress may also play a role, because ruptured plaques are typically located at branch points in the coronary circulation (9).

Role of Oxidative Injury

Inflammation plays a major role in both the genesis and rupture of atherosclerotic plaques (10). The damaging effects of inflammation are largely due to the oxidative actions of "reactive oxygen species", as described in Chapter 17 (see Figure 17.1), and this implicates oxidative injury as a major participant in coronary artery disease. The principle culprit in this scenario appears to be *myeloperoxidase* (MPO), an enzyme released by leukocytes that generates hypochlorite (the active ingredient in household bleach), and oxidizes lipoproteins in atherosclerotic plaques (11). Clinical studies have shown a direct correlation between plasma levels of MPO and the presence and severity of coronary artery disease (12,13), and autopsy studies in humans have shown extensive staining for MPO at the rupture site of coronary artery plaques (13). These observations suggest that inhibition of MPO is a potential treatment modality for coronary artery disease.

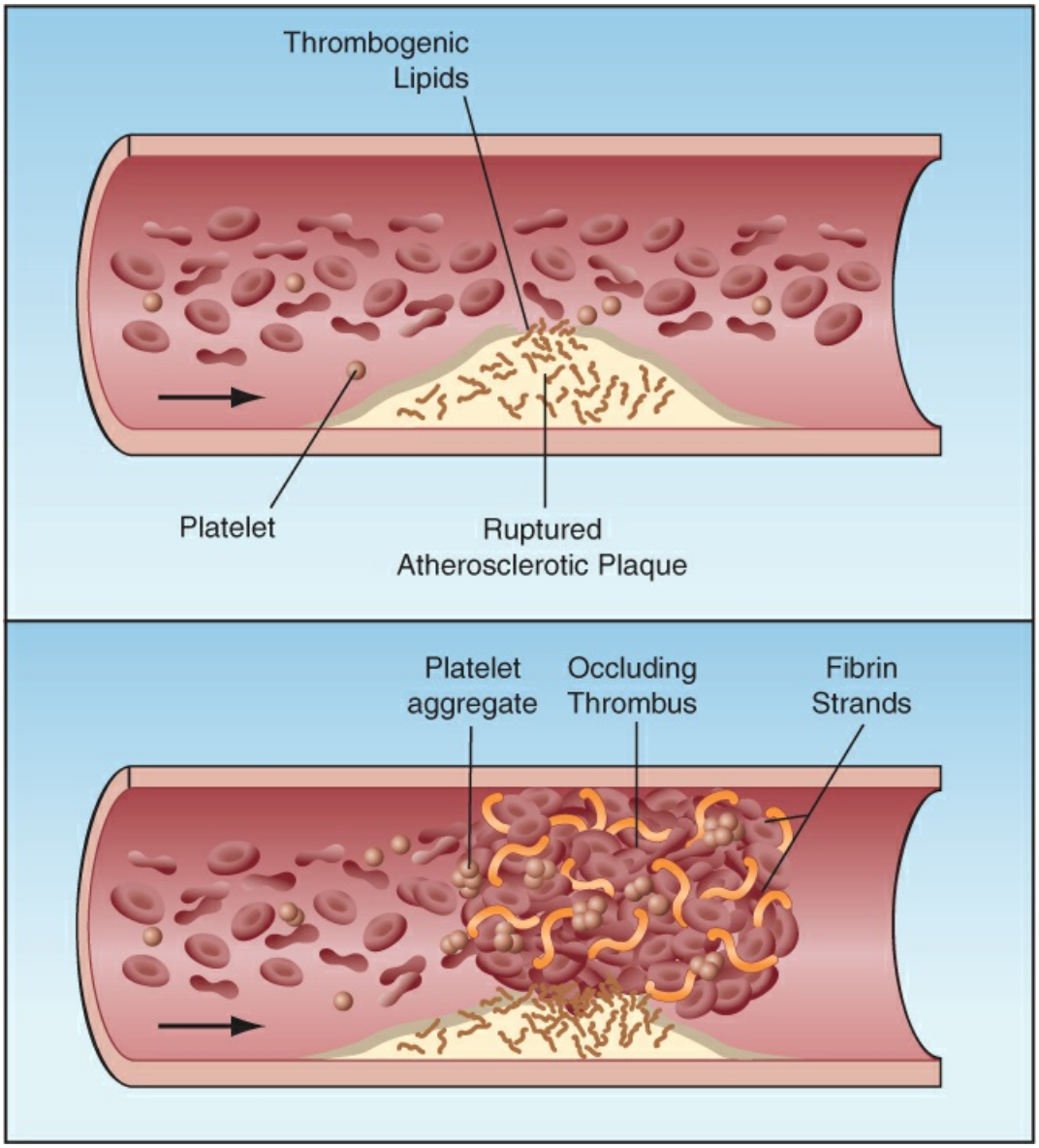


FIGURE 20.1 Pathogenesis of acute coronary syndromes. Rupture of an atherosclerotic plaque releases thrombogenic lipids that activate platelets and clotting factors (upper panel), resulting in

the formation of an occlusive thrombus (lower panel).

Clinical Syndromes

Acute coronary thrombosis produces three distinct clinical syndromes (which are the acute coronary syndromes, or ACS), which are classified by the presence or absence of ST-segment elevation on a 12-lead electrocardiogram (ECG):

. ST-elevation myocardial infarction (STEMI), which is a transmural infarction caused by complete occlusion of the infarct-related artery.

. Non-ST-elevation myocardial infarction (NSTEMI), which is the result of incomplete or partial occlusion of the infarct-related artery.

. Unstable angina (UA), which is not associated with ST elevation on the ECG, and is the result of repetitive on-off episodes of coronary occlusion.

NSTEMI and UA are typically grouped together as “non-ST-elevation acute coronary syndromes”, or NSTE-ACS.

Diagnostic Evaluation

The success of treating ACS is time-dependent, so the diagnostic evaluation must be completed as quickly as possible, The evaluation has three components: the clinical presentation, the 12-lead ECG, and the high-sensitivity troponin assay.

CLINICAL PRESENTATION: The clinical presentation of ACS can vary widely, but about 80% of patients have some type of chest discomfort (e.g., pain, pressure, tightness, etc.) (3,4). The onset is abrupt, and lasts for longer than 15 minutes. The discomfort is a deep sensation that cannot be localized to a specific point, and can involve the shoulders, neck, arms, and abdomen. Patients are often apprehensive, and can complain of nausea, vomiting, and dyspnea.

ACS is unlikely when chest pain is sharp or fleeting, or can be localized to a precise point, and also if the pain occurs during inspiration, or can be elicited by body movements or chest percussion. Of particular note, *chest pain that is relieved by nitroglycerin is not evidence of myocardial ischemia, since nitroglycerin can also relieve chest pain from esophageal spasm* (14).

The initial evaluation may also reveal evidence of acute heart failure or cardiogenic shock. These complications are not considered in this chapter, but are described in detail in Chapters 16 and 18.

ELECTROCARDIOGRAM: A 12-lead electrocardiogram (ECG) *should be obtained within 10 minutes of the first patient contact* (2). Some of the ECG changes in ACS are shown in Table 20.1 ECG evidence of ST-elevation MI (STEMI) merits emergency reperfusion therapy (described later). NSTEMI and UA (NSTE-ACS) may be accompanied by ST depressions or T-wave inversions, but the ECG can also be normal in these conditions. Finally, ischemic changes in the ST segment can be masked by a bundle branch block or a paced rhythm, and when coronary ischemia is suspected, the presence of these ECG abnormalities is managed like a STEMI (i.e., with emergent reperfusion therapy).

TROPONIN ASSAY: Plasma levels of cardiac troponin (cTn) are used to detect the presence of myocardial cell injury, and a high-sensitivity assay (hs-cTn) can detect elevations of plasma cTn as early as 3 hours after the onset of symptoms (15). There are several commercial hs-cTn assays, and the normal or reference levels differ for each assay, and can differ for each hospital. The following protocol is recommended for hs-cTn levels (2–6).

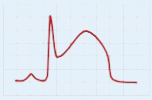
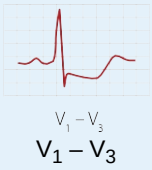
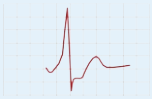
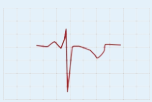
. Plasma levels of hs-cTn are measured at the time of presentation, and again one hour later.

. Myocardial necrosis is likely if the initial hs-cTn level is elevated (usually above the 99% upper reference level for the assay), and there has been at least 3 hours since the onset of symptoms. Conditions other than ischemia can cause myocardial injury, hence a repeat hs-cTn level at one hour is used to determine if the myocardial injury is ischemic in origin (see next).

. A significant change (usually >10%) in the second hs-cTn level is evidence of acute ischemia (i.e., acute MI).

There are several non-ischemic causes of elevated hs-cTn levels (e.g., cardiomyopathy, sustained tachycardia, heart failure, pulmonary hypertension, and even sepsis) (2,3) but these conditions should not cause an acute change in the hs-cTn levels. However, patients with markedly elevated hs-cTn levels are usually admitted to the hospital for further testing.

TABLE 20.1 ECG Changes in Acute Coronary Syndromes

Condition	Pattern	Criteria
STEMI		ST elevation at the J point in ≥2 contiguous leads: either ≥1.5 mm (females) or ≥2.0 mm (males) in V_2–V_3, or ≥1 mm in the other leads.
Posterior STEMI	 $V_1 - V_3$	ST depression in V_1–V_3 with a positive T wave.
NSTE-ACS		J point depression ≥0.5 mm in V_2–V_3, or ≥1 mm in all other leads. ST segment can be horizontal or downsloping.
NSTE-ACS		T wave inversion >1 mm in ≥5 leads, including I, II, aVL, and V_2–V_6.

From Reference 5.

REPERFUSION STRATEGIES

When the likelihood of an acute coronary occlusion is very high using the evaluation just described, the next step is to determine the appropriate strategy for restoring flow in the occluded artery. Three methods are available for coronary reperfusion:

. Percutaneous coronary intervention (PCI), which involves coronary angiography (to identify the obstruction), balloon angioplasty (to restore patency), and placement of a stent (to prevent re-occlusion). This is the standard reperfusion method.

. Thrombolytic drug therapy, which is a less effective alternative when PCI is not available.

. Coronary artery bypass surgery, which is reserved for cases where PCI is not warranted, or is not successful.

Strategies

The reperfusion strategies for ACS are based on the presence or absence of ST-elevation on the ECG, and the availability of PCI. The following recommendation are from the most recent clinical practice guidelines (2,3,5–7).

ST-Elevation MI

The management outlined below is for patients with ECG evidence of STEMI, and for cases where myocardial ischemia is likely and there is a bundle branch block on the ECG.

. The optimal management is emergency PCI, performed within 90–120 minutes of hospital arrival (i.e., the "door-to-balloon" time) (2,6).

. If PCI is unavailable, patients should be transferred immediately to a PCI-capable hospital, with a target door-to-balloon time of 120 minutes. If the transfer time is expected to exceed 120 minutes, thrombolytic therapy can be given prior to the transfer, and should be initiated within 30 minutes of hospital arrival (i.e., the "door-to-needle" time) (6).

. Coronary artery bypass surgery is reserved for cases where PCI fails to establish reperfusion and there is ongoing ischemia.

DOOR-TO-BALLOON TIME: The negative impact of delays in performing balloon angioplasty is shown in Figure 20.2 (16). Note that the mortality rate is significantly increased when the time from hospital arrival to coronary angioplasty (the "door-to-balloon" time) exceeded 120 minutes. The American Heart Association recommends 90 minutes as the target door-to-balloon time (6), which allows a 30-minute buffer period.

INTERHOSPITAL TRANSFERS: Less than 30% of hospitals in the United States are equipped to perform PCI (17), and about one of every four patients with a STEMI is brought to a non-PCI hospital (18). When this occurs, transfer to a PCI-capable hospital can provide a survival benefit if the total door-to-balloon time does not exceed 120 minutes (19). When long delays are anticipated, thrombolytic therapy can be used as a bridge to PCI (2,6).

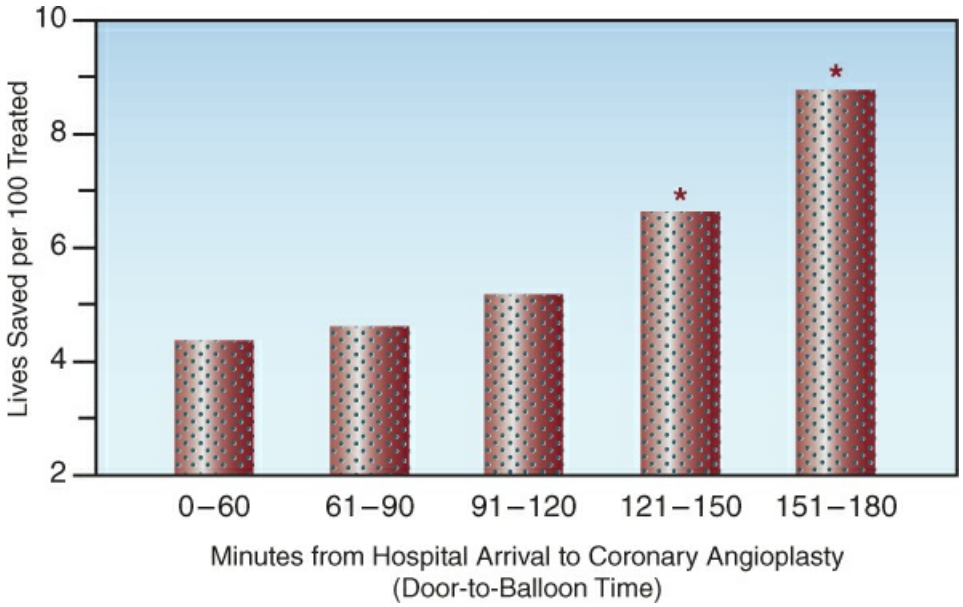


FIGURE 20.2 Mortality rate in relation to the time from hospital arrival to coronary angioplasty in patients with STEMI. Asterisks indicate a significant difference compared to the initial time period (0–60 min). Adapted from data in Reference 16.

Non-ST-Elevation ACS

. Urgent (as soon as possible) PCI is advised for cases of non-ST-elevation MI (NSTEMI) that are complicated by hemodynamic instability, cardiogenic shock, acute heart failure, or persistent chest pain (2,5). Otherwise, PCI can be performed 24–72 hours after presentation (5).

. Thrombolytic therapy has no survival benefit in NSTEMI, and is not used as an alternative to PCI.

. Patients with unstable angina who are hemodynamically stable and devoid of pain may not require PCI during hospitalization.

Thrombolytic Therapy

Thrombolytic therapy is less effective than PCI (19), and is limited to uncomplicated cases of STEMI where PCI is not immediately available. The following are additional limiting factors for thrombolytic therapy.

. The survival benefit of thrombolytic therapy is time-dependent; i.e., it is greatest in the first few hours after symptom onset, and then gradually declines and is lost after 12 hours (20). This is demonstrated in Figure 20.3, and is the basis for the recommendation that *thrombolytic therapy is not advised if more than 12 hours have elapsed from symptom onset* (6).

. In addition to time constraints, the use of thrombolytic therapy is limited by the risk of bleeding. Absolute and relative contraindications to thrombolytic therapy are presented in Chapter 47.

Thrombolytic Agents

Thrombolytic agents act by converting plasminogen to plasmin, which then breaks fibrin strands into smaller subunits. The thrombolytic agents approved for clinical use, are shown in Table 20.2. These agents act on the plasminogen that is bound to fibrin strands in the blood clot, and this limits the extent of systemic fibrinolysis, and reduces the risk of troublesome bleeding. The lytic agents in Table 20.2 are equally capable of restoring patency in occluding coronary arteries (6).

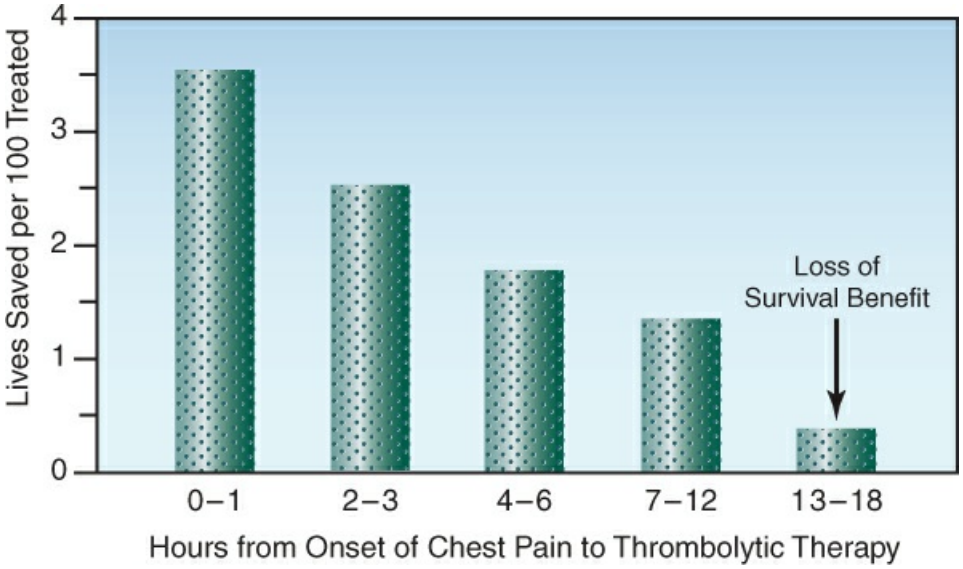


FIGURE 20.3 The survival benefit of thrombolytic therapy in relation to the time elapsed from the onset of chest pain. Data from 45,000 patients with STEMI or left bundle branch block in Reference 20.

. *Alteplase* (Activase) is a recombinant tissue plasminogen activator (tPA) that was the first clot-specific fibrinolytic agent approved for clinical use. However, it is no longer favored because it is relatively slow-acting (21), and requires 90 minutes to complete the dosing regimen.

. *Reteplase* (Retavase) is a recombinant variant of tPA that is given as two bolus doses over a 30-minute period. It produces more rapid clot lysis than alteplase (21), but clinical trials show no survival advantage (22).

. *Tenecteplase* (TNK-tPA) is another variant of tPA that is given as a single IV bolus, and produces more rapid clot lysis than reteplase (23). It is currently the most popular thrombolytic agent, but has no proven survival advantage (24).

TABLE 20.2 Thrombolytic Therapy for Acute Coronary Occlusion

Agent	Dosing Regimen	Patency Rate at 90 min.
Alteplase (tPA)	15 mg IV bolus, then 0.75 mg/kg (not >50 mg) over 30 min, then 0.5 mg/kg (not >35 mg) over 60 min. Max dose: 100 mg over 90 min.	73–84%
Reteplase (rPA)	10 Units as IV bolus and repeat in 30 min.	84%

Tenecteplase (TNK-tPA)	Single IV bolus: 30 mg for wt. <60 kg, 35 mg for 60–69 kg, 40 mg for 70–79 kg, 45 mg for 80–89 kg, and 50 mg for ≥90 kg.	85%

From Reference 6.

Major Bleeding

Thrombolytic therapy for ACS is complicated by significant bleeding (i.e., requires blood transfusions) in about 10% of cases, and life-threatening bleeding (shock or intracranial hemorrhage) occurs in about 1% of cases (25). The bleeding is associated with low plasma fibrinogen levels (usually <100 mg/dL) and can be treated with concentrated fibrinogen products such as cryoprecipitate or fibrinogen concentrates (see the last section of Chapter 13). The use of antifibrinolytic agents such as tranexamic acid is discouraged because of the risk of thrombosis (26).

CARDIOPROTECTIVE MEASURES

The following measures are aimed at improving the balance between myocardial O_2 supply and O_2 demand, and are initiated when myocardial ischemia is first suspected (sometimes in the pre-hospital setting). These measures are summarized in Table 20.3.

Oxygen

Despite a long history of routine use in ACS, supplemental O_2 provides no benefit in patients with ACS who have a normal arterial O_2 saturation (i.e., SaO_2 ≥90%) (27). As a result, the current recommendation is to *use supplemental oxygen only in patients who are hypoxemic; i.e., have an SaO_2 <90%* (2,5,6). More compelling reasons to avoid the unnecessary use of oxygen in ACS are as follows:

. Oxygen promotes vasoconstriction in the coronary arteries, and can decrease coronary blood flow in patients with coronary artery disease (28).

. Reactive oxygen species are implicated in the myocardial injury that follows coronary reperfusion (29).

(For more on the dark side of oxygen, see Chapter 25.)

TABLE 20.3 Cardioprotective Measures

Agent	Dosing Regimens and Comments
Oxygen	Dosing: Whatever is needed to maintain an SaO_2 ≥90%. Comment: Use supplemental O_2 judiciously, because it promotes coronary artery vasoconstriction.
Nitroglycerin	Dosing: For chest pain: 0.4 mg sublingual or by mouth spray every 5 min x 3, as needed. For recurrent pain, high BP or CHF: infuse at 5 µg/min initially, then titrate upward to desired end-point. Comment: Avoid in RV infarction, aortic stenosis, and for 24–48 hrs after a dose of phosphodiesterase inhibitors. Tachyphylaxis is common with prolonged (>24 hrs)

	infusions.
Morphine	Dosing: 4–8 mg IV, and follow with 2–8 mg IV every 5–15 min as needed. Comment: Reduces antiplatelet effect of P2Y12 inhibitors, but clinical significance is uncertain.
Metoprolol	Dosing: 4–8 mg IV, and follow with 2–8 mg IV every 5–15 min as needed. Comment: Avoid early use of β-blockers in acute heart failure, but not after the condition stabilizes. β-blockers contraindicated in cocaine-related ischemia.

Relieving Chest Pain

Relieving chest pain helps to alleviate unwanted cardiac stimulation from anxiety-induced adrenergic hyperactivity.

Nitroglycerin

Nitroglycerin is given as a sublingual tablet or aerosol spray to relieve chest pain, and a total of 3 doses can be given in 5-minute intervals if necessary. (The mechanism of pain relief with nitroglycerin is unclear; i.e., it is often attributed to its vasodilator effects, but other vasodilators do not relieve ischemic chest pain.) If the pain recurs, a nitroglycerin infusion can be started using the dosing regimen in Table 20.2. Nitroglycerin infusions can also benefit cases of ACS that are accompanied by hypertension or decompensated heart failure.

CONCERNS: Nitroglycerin is not advised in patients with right ventricular infarction (because the venodilator effects of nitroglycerin can be counterproductive in this condition), severe aortic stenosis, or in patients who have received a phosphodiesterase inhibitor for erectile dysfunction within the past 24–48 hours (because of the risk of hypotension) (2,5,6). (Complications of nitroglycerin infusions are described in Chapter 18.)

Morphine

Morphine is the drug of choice for chest pain that is refractory to nitroglycerin. Morphine also has a sedating effect, but the addition of a benzodiazepine (e.g., midazolam, 0.01 mg/kg IV) is sometimes needed to relieve anxiety.

CONCERNS: The complications of opioids are described in Chapter 6. Morphine (and fentanyl) can also impair the antiplatelet effects of the P2Y12 inhibitors used in ACS (see later), but the clinical significance of this effect is unproven (2).

β-Receptor Antagonists

β-blockers have several actions that reduce myocardial O_2 demand, and are usually started in the first 24 hours after diagnosis of ACS. The agent most often studied in ACS is *metoprolol*, and the dosing recommendations are shown in Table 20.3. Intravenous metoprolol can be useful in patients with troublesome tachycardia or hypertension, or prior to PCI in patients with STEMI (30).

When to Avoid

Traditional contraindications to β-blockers include bradycardia, hypotension, and high-degree

AV block. Other caveats for ACS are as follows:

. Early treatment with β-blockers is not advised in ACS associated with acute heart failure (2,5,6), but after the condition is stabilized, β-blockers are recommended for long-term therapy of heart failure with reduced ejection fraction (see Table 18.5).

. When the systolic BP is <120 mm Hg, β-blockers increase the risk of cardiogenic shock (31).

. β-blockers are contraindicated in cocaine-induced myocardial ischemia because they promote unopposed α-adrenergic vasoconstriction (32).

ANTITHROMBOTIC MEASURES

Antithrombotic measures are used to prevent growth of an existing thrombus (prior to reperfusion), and to reduce the risk of recurrence (after reperfusion).

Antiplatelet Agents

Antiplatelet therapy has a more important role in coronary thrombosis than in other thrombotic conditions (probably because of the vascular manipulation involved in coronary angioplasty). The antiplatelet agents and recommended dosing regimens for ACS are shown in Table 20.4.

Aspirin

Aspirin produces irreversible inhibition of platelet aggregation by inhibiting thromboxane production. It has a proven survival benefit in ACS (1 life saved per 42 treated) (33), and is given to all patients with suspected ischemia, as soon as possible after first patient contact. The initial dose is given as a chewable (non-enteric coated) formulation, and is intended for buccal absorption (i.e., should not be swallowed). Rectal aspirin is advised when oral delivery is not possible. Aspirin is continued indefinitely in cases of ACS, often together with a second antiplatelet agent (see next). For patients with an aspirin allergy, clopidogrel is a suitable alternative.

TABLE 20.4 Antiplatelet Measures for Acute Coronary Thrombosis

Agent	Dosing Regimen
Aspirin	162–325 mg (in chewable form) at first patient contact, then daily dose of 81 mg (for dual anti-platelet R_x) or 325 mg. If aspirin allergy, use clopidogrel.
P2Y12 Inhibitors	
Clopidogrel (Plavix)	PO: 300–600 mg initially, then 75 mg daily
Ticagrelor (Brilinta)	PO: 180 mg initially, then 90 mg twice daily
Prasugrel (Effient)	PO: 60 mg initially, then 10 mg daily
GP IIb-IIIa	IV: 180 µg/kg bolus (max 22.6 mg), then 2 µg/kg/min (max 15 mg/hr) with second bolus 10 min

Inhibitors	after first. Reduce infusion rate by 50% for Cr CL <50 mL/min.
Eptifibatide (Integrilin)	IV: 25 μg/kg (bolus), then 0.15 μg/kg/min. Reduce infusion rate by 50% for CrCL<30 mL/min.
Tirofiban (Aggrastat)	

From the clinical practice guidelines in References 2, 5, and 6.

P2Y12 Inhibitors

P2Y12 inhibitors block the platelet surface receptors that mediate ADP-induced platelet aggregation. The drugs available for use include clopidogrel, prasugrel and ticagrelor, and their dosing regimens are shown in Table 20.4. (Cangrelor is an intravenous P2Y12 inhibitor that is rarely used, and is not included here.) *A P2Y12 inhibitor should be added to aspirin (dual antiplatelet therapy) for all patients with ACS, and the first dose should be given prior to PCI* (2,5,6).

CLOPIDOGREL (PLAVIX): Clopidogrel is a prodrug that is converted to its active form in the liver, and this results in variable antiplatelet effect. Activation in the liver is also blocked by proton pump inhibitors (34), but the clinical significance of this is questioned. Once activated, clopidogrel causes irreversible platelet inhibition, and the drug should be stopped at least 5 days before a major surgical procedure. This prolonged effect is also reason to avoid clopidogrel if coronary bypass surgery is imminent.

TICAGRELOR (BRILINTA): Ticagrelor is a direct-acting drug that provides more potent and more consistent P2Y12 inhibition than clopidogrel, and it is superior to clopidogrel for improving outcomes (mortality rate, reinfarction) in patients with ACS (35). There is, however, an increased risk of intracranial hemorrhage (ICH) with ticagrelor (35), and the drug is contraindicated in patients with a prior ICH.

PRASUGREL (EFFIENT): Prasugrel is a prodrug like clopidogrel, but is more effective as an antiplatelet agent, and is superior to clopidogrel for preventing stent thrombosis and recurrent ischemia (36). However, the bleeding risk is higher with prasugrel (36), and the drug is contraindicated in patients with recent stroke or TIA (2,5,6).

Glycoprotein Receptor Antagonists

When platelets are activated, specialized glycoprotein receptors on the platelet surface (named IIb and IIIa) change their configuration and begin to bind fibrinogen. This allows fibrinogen molecules to form bridges between adjacent platelets, which promotes platelet aggregation. Glycoprotein receptor antagonists (also called *IIb/IIIa inhibitors*) block fibrinogen binding to activated platelets and inhibit platelet aggregation. These drugs are the most potent antiplatelet agents available, and are sometimes referred to as the *superaspirins*.

The IIb/IIIa inhibitors include *eptifibatide* (Integrilin), and *tirofiban* (Aggrastat). They are given by intravenous infusion, using the dosing regimens in Table 20.4. These drugs are used in high-risk patients who receive emergent PCI, and are given just before or at the start of the procedure. They are managed primarily by invasive cardiologists, and are not described further here.

Anticoagulant Therapy

Anticoagulation with heparin is recommended for all patients with ACS, and is started at the time of diagnosis. The options are as follows:

. Unfractionated heparin is preferred for patients who receive emergent PCI or thrombolysis. The recommended dose is 60 Units as an IV bolus (maximum 4,000 Units), followed by an infusion of 12 Units/kg/hr (maximum 1,000 Units/hr) initially, titrated to achieve an activated PTT(aPTT) of 1.5–2 times control (3,5). This is typically continued for 24–48 hrs.

. Low-molecular-weight heparin can be used when PCI is non-emergent or deferred. The dosing regimen for *enoxaparin* is 30 mg as an IV bolus, followed in 15 minutes by 1 mg/kg by subcutaneous injection every 12 hrs (3,5). (The bolus dose is not recommended in patients older than 75 years of age.) The dose is reduced by 50% (e.g., 1 mg/kg every 24 hours) when the creatinine clearance is <30 mL/min.

. For patients with a history of heparin-induced thrombocytopenia (see Chapter 19), the following alternative regimens are available (6):

a. For PCI: *Bivalirudin* (a direct thrombin inhibitor), 0.75 mg/kg as IV bolus, followed by an infusion of 1.75 mg/kg/hr. Reduce infusion rate to 1 mg/kg/hr for creatinine clearance <30 mL/min. Discontinue after successful PCI.

b. For Thrombolytic Therapy: *Fondaparinux* (factor Xa inhibitor), 2.5 mg as IV bolus, and on following day, start 2.5 mg by subcutaneous injection daily until cardiac catheterization. Contraindicated if creatinine clearance <30 mL/min.

LONG-TERM THERAPIES

The treatments summarized here are instituted when patients are clinically stable (e.g., after emergent PCI), and are continued indefinitely, as tolerated.

. High-intensity statin treatment with *atorvastatin*, 80 mg daily, has been shown to reduce the risk of major cardiovascular events following ACS (37), and is recommended for all patients with ACS (5,6).

. Inhibition of the renin-angiotensin-aldosterone (RAA) system is recommended for all patients with ACS, especially patients with hypertension, anterior STEMI, or heart failure associated with reduced ejection fraction (6). At the present time, the favored drug for this purpose is *sacubitril/valsartan* (Entresto) (38), a combination drug with an angiotensin receptor blocker, and a drug (sacubitril) that inhibits neprilysin (an enzyme that degrades natriuretic peptides). The dosing of this drug is shown in Table 18.5. RAA inhibitors are contraindicated in patients with a history of angioedema (from any source), and they should be used cautiously in patients with renal impairment who are prone to hyperkalemia.

. Long-term treatment with β-blockers is recommended for all patients with ACS, especially in cases of heart failure associated with reduced ejection fraction (see Chapter 18). Metoprolol is the β-blocker most often used in this setting, and the dosing recommendations are shown in Table 20.3.

ACUTE AORTIC DISSECTION

At the outset, the following points about acute dissection of the ascending aorta deserve emphasis:

. The clinical presentation can mimic, or include, ACS.

. This condition is a surgical emergency, and about 60% of patients will perish without prompt surgical intervention (39).

. One of every three cases is missed (40).

Pathophysiology

Aortic dissection occurs when a tear in the aortic intima allows blood to dissect between the intimal and medial layers of the aortic wall, creating a false lumen. This process can be the result of atherosclerotic damage, or accelerated degradation of the aortic wall from a genetic disorder (e.g., Marfan's syndrome). The dissection can originate in the ascending or descending aorta, and can propagate in antegrade and retrograde directions. When a dissection involves the ascending aorta between the aortic valve and the brachiocephalic artery (type A dissection), retrograde propagation can cause aortic valve insufficiency, coronary artery occlusion, and pericardial tamponade,while antegrade propagation can lead to neurologic deficits from occlusion of the aortic arch vessels.

Clinical Presentation

The most common complaint is the abrupt onset of sharp chest pain, which may be described as "ripping" or "tearing", and can be substernal (ascending aortic dissection) or in the back (descending aortic dissection). Only 5% of patients with acute aortic dissection are pain-free (41). Most importantly, *the chest pain can subside spontaneously for hours to days* (42,43), and the return of chest pain is often a sign of impending aortic rupture. *The spontaneous resolution of chest pain is an important source of missed diagnoses.*

Clinical Findings

The most frequent clinical findings are hypertension (50% of patients) and aortic insufficiency (50% of patients) (42,44). Unequal pulses in the upper extremities (from obstruction of the left subclavian artery) is a classic but infrequent finding (15% of cases) (42). The chest x-ray can show mediastinal widening (60% of cases) (42), but normal chest x-rays are reported in up to 20% of cases (41). The ECG can show ischemic changes (15% of cases) but it is normal in 30% of cases (41). Because of the limited sensitivity of clinical findings, additional imaging studies are required for the diagnosis.

Diagnostic Imaging

The diagnosis of aortic dissection requires one of four imaging modalities (43): magnetic resonance imaging (MRI) (sensitivity and specificity 98%), transesophageal echocardiography (sensitivity 98%, specificity 77%), contrast enhanced computed tomography (sensitivity 94%, specificity 87%), and aortography (sensitivity 88%, specificity 94%). As indicated, *MRI is the*

most sensitive and specific imaging modality for the diagnosis of aortic dissection, but CT angiography is also acceptable.

The CT image in Figure 20.4 shows a dissection of the ascending aorta. The small arrows point to the intimal flap that separates the dissecting blood in the wall of the aorta (false lumen) from blood in the true lumen of the aorta. The presence of this flap distinguishes an aortic dissection from a saccular aneurysm of the aorta.

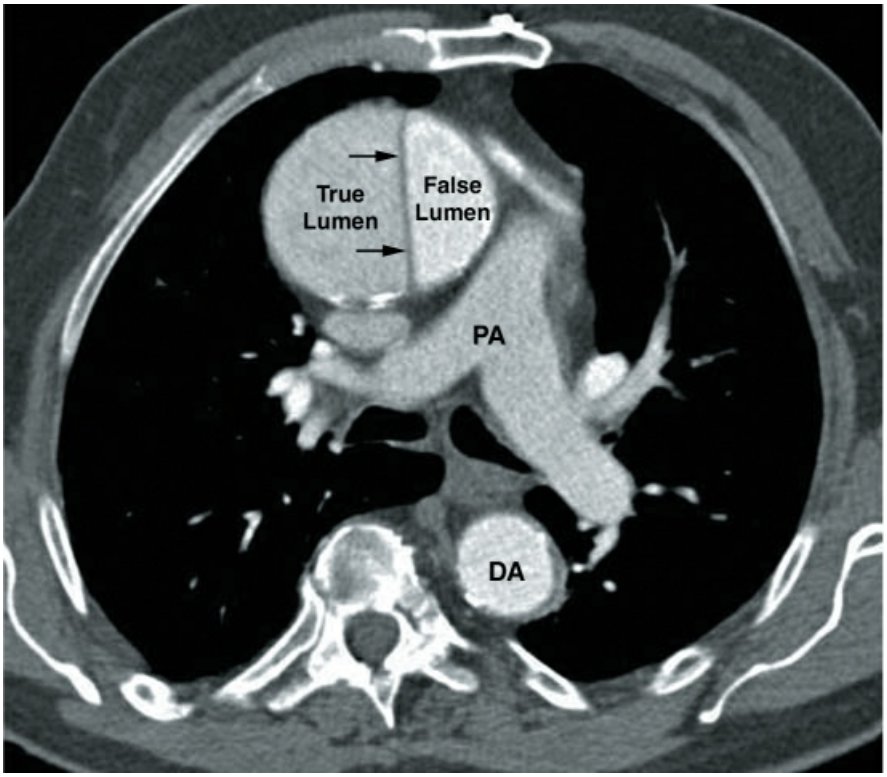


FIGURE 20.4 Contrast-enhanced CT image showing an acute dissection in the ascending aorta. The intimal flap that separates the true and false lumens (indicated by the small arrows) distinguishes an aortic dissection from a saccular aneurysm. PA = pulmonary artery, DA = descending aorta.

Management

The management goals in acute, type A aortic dissection include control of hypertension (to prevent aortic rupture), relief of pain (to assist in management of blood pressure), and prompt surgical intervention (the treatment of choice).

TABLE 20.5 Antihypertensive Therapy for Acute Aortic Dissection

Drug	Dosing Regimens and Comments
Esmolol	Dosing: 500 µg/kg as IV bolus, then infuse at 50 µg/kg/min and increase rate in increments of 25 µg/kg/min to desired BP, or to maximum of 200 µg/kg/min. Give a repeat bolus dose before each increment in infusion rate. Comment: Ultra rapid-acting β-blocker that can be rapidly titrated to achieve the desired BP. Not advised in the presence of acute heart failure.

Labetalol	Dosing: 20 mg IV over 2 min, then 20–40 mg IV every 10 min as needed, or infuse at 1–2 mg/min and titrate to desired BP. Max. cumulative dose is 300 mg. Comment: A combined α- and β-blocker that is used as monotherapy. Avoid use in acute heart failure.
Metoprolol	Dosing: 5mg as IV bolus and repeat in 5 min x 2, if needed. Continue with 5–10 mg IV every 4–6 hrs, as needed. Comment: Best suited for initial β-blockade when vasodilators are used.
Nicardipine	Dosing: Infuse at 5mg/hr, and increase by 2.5 mg/hr every 5 min as needed to maximum infusion of 15 mg/hr. Comment: Use in combination with a β-blocker.
Nitroprusside	Dosing: Infuse at 0.2 µg/kg/min and titrate upward every 5 min to the desired effect. Effective dose is typically 2–5 µg/kg/min, but avoid prolonged infusions at >3 µg/kg/min to reduce the risk of cyanide toxicity. Can add thiosulfate (500 mg) to the infusate (binds cyanide released by nitroprusside. Comment: Use in combination with a β-blocker. Do not use in patients with hepatic or renal failure, or in the presence of coronary ischemia.

Dosing regimens are manufacturer's recommendations.

Antihypertensive Therapy

There is one major caveat for blood pressure control in aortic dissection; i.e., *the reduction in blood pressure should NOT be accompanied by tachycardia or an increase in cardiac output*, as these conditions will augment the shear forces that promote dissection. As a result, β-*blockers are preferred* for blood pressure control in aortic dissection, and vasodilators (e.g., nicardipine) should only be used in combination with β-blockers (39). The drug regimens that are used in aortic dissection are shown in Table 20.5. Esmolol is the preferred β-blocker because it is rapidly titratable. The goal of antihypertensive management in aortic dissection is a systolic pressure of 120 mm Hg, although pressures down to 90 mm Hg are usually tolerated (39).

Pain Relief

Pain can aggravate an acute aortic dissection by activating the sympathetic nervous system, which promotes an increase in heart rate, cardiac output, and blood pressure. Thus, pain relief with intravenous opioids is an early goal of management (39).

Surgical Intervention

Open surgical repair of the ascending aorta is the standard of care in patients with acute, type A aortic dissection, and timely intervention is critical, because the mortality rate increases 1–2% per hour after the onset of symptoms (39). If the patient is at a hospital that does not provide acute cardiac surgery, then transfer to another hospital for surgical intervention is imperative. Surgical repair can reduce the mortality rate to as low as 10% (30).

A FINAL WORD

The O_2 Supply-Demand Dogma

The traditional notion that myocardial infarctions are the result of an imbalance between O_2 supply and O_2 demand is misleading, because it implies that conditions like anemia and hypoxemia can cause myocardial infarctions. However, *myocardial infarctions are caused by a blood clot that obstructs a coronary artery, not by conditions that cause a global decrease in myocardial O_2 delivery*.

Ever wonder why acute MIs do not occur in patients with progressive circulatory shock (where O_2 delivery is severely impaired)? Now you have the answer.

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Chapter 21

Cardiac Arrest

When we all think alike, then no one is thinking.

Walter Lippmann (*a*)

In 1960, a report appeared in the *Journal of the American Medical Association* that would eventually change the way we approach the dying process. The report was titled “Closed Chest Cardiac Massage” (1), and it included 5 cases of cardiorespiratory arrest that were successfully managed with chest compressions, electrical shocks, and assisted ventilation. That same year (and without any validation studies), the American Heart Association started a program to educate physicians about closed-chest cardiac resuscitation, which eventually grew to become *cardiopulmonary resuscitation* (CPR). Since its inception, CPR has become a universally mandated practice that is withheld only on request, and requires certification every 2 years to ensure the competence of practitioners. And all this for a treatment modality that fails in most cases, as shown in Table 21.1 (2).

This chapter describes the practical aspects of CPR, and the management that follows a successful resuscitation effort. The recommendations in this chapter are taken from the most recent and most relevant guidelines and instruction manuals on CPR, which are listed in the bibliography at the end of the chapter (3–8).

TABLE 21.1 Cardiac Arrest Data for the United States, 2021

	Out-of-Hospital Cardiac Arrests	In-Hospital Cardiac Arrests
Number	143,018	8,619
Vtach/Vfib	17%	13%
PEA/Asystole	75%	78%
Survived to Hospital Discharge	9%	19%
Survived with Good Functional Status	7%	1%

Data from Reference 2.

BASIC LIFE SUPPORT

The elements of basic life support (BLS) are chest compressions, and periodic lung inflations through a patent upper airway. The priority for these elements is indicated by the popular mnemonic *CAB* (Circulation, Airway, and Breathing).

Time Dependence

One of the major limiting factors in the success of CPR is the narrow time window between the cessation of blood flow and irreversible cell death. The total O_2 content of the adult human body is about one liter, and with a normal O_2 consumption of about 250 mL/min at rest, this leaves only about 4 minutes after the cessation of blood flow until the O_2 content of the body is completely depleted. Thus, *following the cessation of blood flow from a cardiac arrest, anoxic cell death is expected in just 4–5 minutes*. (One exception to this is cold-water drowning, where the cold temperatures will reduce O_2 consumption and prolong the time for anoxic cell injury.) This emphasizes the "need for speed" in initiating CPR.

TABLE 21.2 The Essential Elements of Basic Life Support

1. Chest compressions should begin within 10 seconds of detecting the absence of pulses.
2. Each chest compression should depress the lower third of the sternum by 2–2.4 inches (5–6 cm), and the chest should be allowed to recoil completely before the next compression.
3. The rate of compressions should be 100–120/minute.
4. After 30 chest compressions, 2 lung inflations are delivered (with a bag-mask device) without interrupting the compressions, and this (30:2) cycle is repeated until the patient is intubated.

5. Following intubation, lung inflations are delivered every 6 seconds (10/min) without interrupting chest compressions. However, simultaneous chest compressions and lung inflations should be avoided.

6. Chest compressions should be continued without interruption until a defibrillator is attached to the patient.

7. Each person performing chest compressions should be relieved after 2 minutes, if possible.

From References 3–5, 7.

Overview

The trigger for CPR is the absence of pulses in an unresponsive patient who has minimal or no spontaneous breathing efforts. Chest compressions should begin within 10 seconds of this trigger, using the depth and frequency of compressions shown in Table 21.2. Two lung inflations should be delivered (with a bag-mask device) after every 30 chest compressions, without interrupting the compressions (3–5). After an endotracheal (ET) tube is placed, lung inflations are delivered at 6-second intervals (10/min) without interrupting chest compressions. However, simultaneous chest compression and lung inflation will limit the inflation volume, and should be avoided (4). Finally, an ECG monitor/defibrillator should be attached to the patient as soon as possible.

Chest Compressions

The backbone of BLS is high-quality chest compressions with minimal interruptions. Observational studies have shown that interruptions in chest compressions can account for as much as 50% of the total resuscitation time (9), and prolonged interruptions could contribute to poor outcomes. Current recommendations are to continue chest compressions without interruptions until a defibrillator is attached to the patient. (Thereafter, compressions can be paused to deliver electric shocks, and to check the cardiac rhythm, as described later.)

High-Quality Compressions

High-quality chest compressions are defined as having a depth of 2–2.4 inches (5–6 cm) and a rate of 100 to 120/min, with full chest recoil allowed between compressions (3–5). Estimating the depth of compressions is difficult, especially with a target range of only 0.4 inches. There are devices used for CPR training that measure the depth of compression and provide audio feedback (e.g., using the sometimes irritating prompt, “push harder”), but they are not available for clinical use. Fatigue can influence the depth of compressions, and each person performing compressions should be replaced after 2 minutes, if possible (4,5).

Lung Inflations

Lung inflations are delivered by compressing a self-inflating ventilation bag (e.g., Ambu Respirator) that fills with oxygen. The recommended volume for each lung inflation is 500–600 mL, or whatever produces a visible rise in the chest wall (4). However, inflation volumes are not monitored during “bagged ventilation”, and large inflation volumes are common during CPR (10), which can be damaging for the lungs (similar to “ventilator-induced lung injury”, which is described in Chapter 24). Closer adherence to the recommended inflation volumes is possible if the volume capacity of the inflation bags in known. For example, if the inflation bag has a volume capacity of 1 liter, compressing the bag until it is about half full will deliver a volume of

about 500 mL. (The volume capacity of most adult ventilation bags is 1 to 2 liters.) An alternative approach is to use one hand to compress the ventilation bag, which delivers a volume of about 600 to 700 mL (personal observation), and is unlikely to produce troublesome lung inflations.

Rapid Lung Inflations

Rapid lung inflations are common during CPR (11,12), and average rates of 30 inflations/min (3 times the recommended rate) have been reported (12). Rapid breathing is problematic because there is insufficient time for the lungs to empty, which leads to progressive hyperinflation and positive end-expiratory pressure (PEEP). The PEEP that is produced by rapid breathing is called "intrinsic PEEP", and is described in detail in Chapter 23. The increase in mean intrathoracic pressure from PEEP has two deleterious effects: 1) it reduces venous return to the heart, which limits the ability of chest compressions to augment cardiac output, and 2) it reduces coronary perfusion pressure (11), which is an important determinant of outcome in cardiac arrest. For these reasons, avoiding rapid inflation rates will increase the chances for a favorable outcome with CPR.

Vascular Access

Vascular access should be established without interrupting chest compressions. Peripheral venous access is considered suitable (4), but intraosseous access is often favored because it is easy to establish without interrupting chest compressions, and is more secure than a peripheral vein catheter. (See Chapter 1 for a description of intraosseous access.)

ADVANCED LIFE SUPPORT

Advanced cardiovascular life support (ACLS) includes electrical cardioversion (defibrillation) and the use of drugs that support the resuscitation attempt. This approach divides the management of cardiac arrest into two pathways: one for the management of ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT), and the other for pulseless electrical activity (PEA) and asystole.

VF and Pulseless VT

The principal intervention for VF and pulseless VT is electrical "defibrillation", and hence these arrhythmias are referred to as "shockable rhythms".

Defibrillation

Electrical cardioversion that uses asynchronous shocks (i.e., not timed to the QRS complex) is called *defibrillation*, and it is one of the few interventions that improves survival in cardiac arrest victims. However, the survival benefit is time-dependent. This is shown in Figure 21.1, which is from a study of the relationship between survival and the time (from collapse) to defibrillation in cardiac arrests associated with VF or VT (13). Note that 40% of patients survived when the first shock was delivered 5 minutes after the arrest, while fewer than 10% of patients survived if defibrillation was delayed until 20 minutes after the arrest.

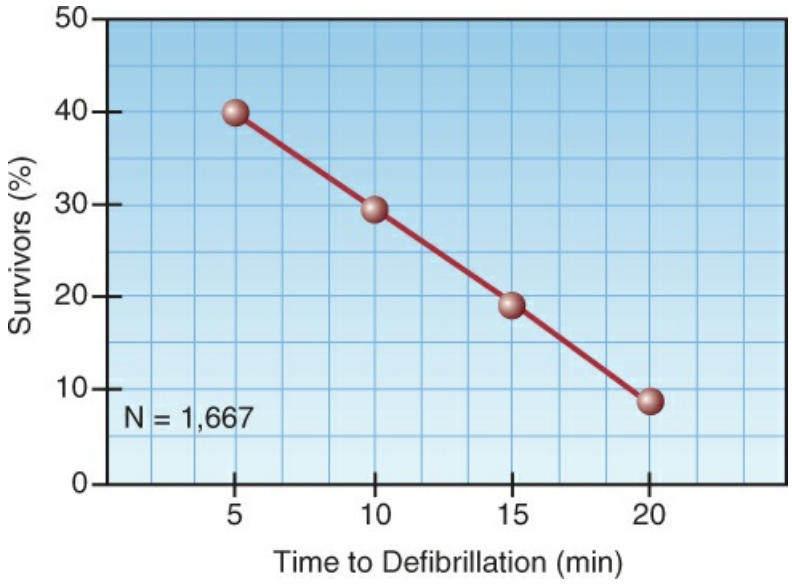

FIGURE 21.1 Relationship between survival and time (from collapse) to first defibrillator shock in 1,667 out-of-hospital cardiac arrests associated with VF or pulseless VT. Data from Reference 13.

IMPULSE ENERGY: Modern defibrillators deliver biphasic shocks (which convert VF and VT at lower energy levels than monophasic shocks), and the effective energy level can vary from as low as 100 J to as high as 360 J, with higher energy levels needed for resistant or recurrent episodes of VF/VT (14). Automated external defibrillators (AEDs) usually deliver fixed-energy shocks, while other defibrillators either have a pre-selected energy level for shocks, or allow the user to select the desired energy level.

Management Algorithm

The ACLS algorithm for cardiac arrest in adults is shown in Figure 21.2 (8), and the left side of the flow diagram indicates the management when the initial rhythm is VF or VT. The major features of the management are summarized below.

. The management includes a series of 3 defibrillation attempts, if needed. The initial shock is usually 120–200 J for biphasic shocks (or is manufacturer-recommended). If this is ineffective, a higher energy level can be used for subsequent shocks, if allowed by the defibrillator.

. Chest compressions are paused when the defibrillation shock is delivered, and are resumed immediately thereafter. At least 2 minutes of uninterrupted chest compressions are recommended after defibrillation before checking the post-shock rhythm.

. If a second defibrillation is needed, *epinephrine* is started using a bolus dose of 1 mg (intravenous or intraosseous) every 3–5 minutes for the duration of the resuscitation effort.

. If a third defibrillation is needed, *amiodarone* is administered as a bolus dose of 300 mg (IV or IO), which can be followed by a second dose of 150 mg, if needed. If amiodarone is not available, *lidocaine* can be given in a initial dose of 1–1.5 mg/kg (IV or IO), followed by 0.5–0.75 mg/kg every 5–10 min as needed, to a maximum dose of 3 mg/kg (8).

SHOCK-RESISTANT CASES: Failure of three defibrillation attempts to convert VT and VF has a

very poor prognosis, with a satisfactory outcome in only 5% of cases (15). Improved outcomes have been reported in shock-resistant VF/VT that is managed with emergency extracorporeal life support (ECMO) (16), and this approach is certainly a consideration if ECMO is available on a 24-hour basis.

Asystole / PEA

The management of cardiac arrest associated with pulseless electrical activity (PEA) and ventricular asystole is shown on the right half of the ACLS algorithm in Figure 21.2. The major intervention is vasopressor therapy with epinephrine using the same dosing regimen used for VF and pulseless VT. Defibrillation is not attempted unless the cardiac rhythm changes to VF or VT.

Reversible Causes of PEA

PEA has potentially reversible causes, which can be identified by the letter "T": i.e., Tension pneumothorax, pericardial Tamponade, venous Thromboembolism, and Thrombotic occlusion of the coronary arteries. Although there is little time for a diagnostic workup during a cardiac arrest, point-of-care ultrasound can be a valuable aid in uncovering some of these conditions (see later).

Epinephrine

Epinephrine is the only circulatory-support drug that is used for CPR. Although it has been shown to increase the rate of return of spontaneous circulation (17), the impact on survival is not clear. Most studies show no improvement in survival associated with epinephrine (17,18), but there is one study that shows an increase in survival at 30 days (19), although many of the survivors were not mentally intact.

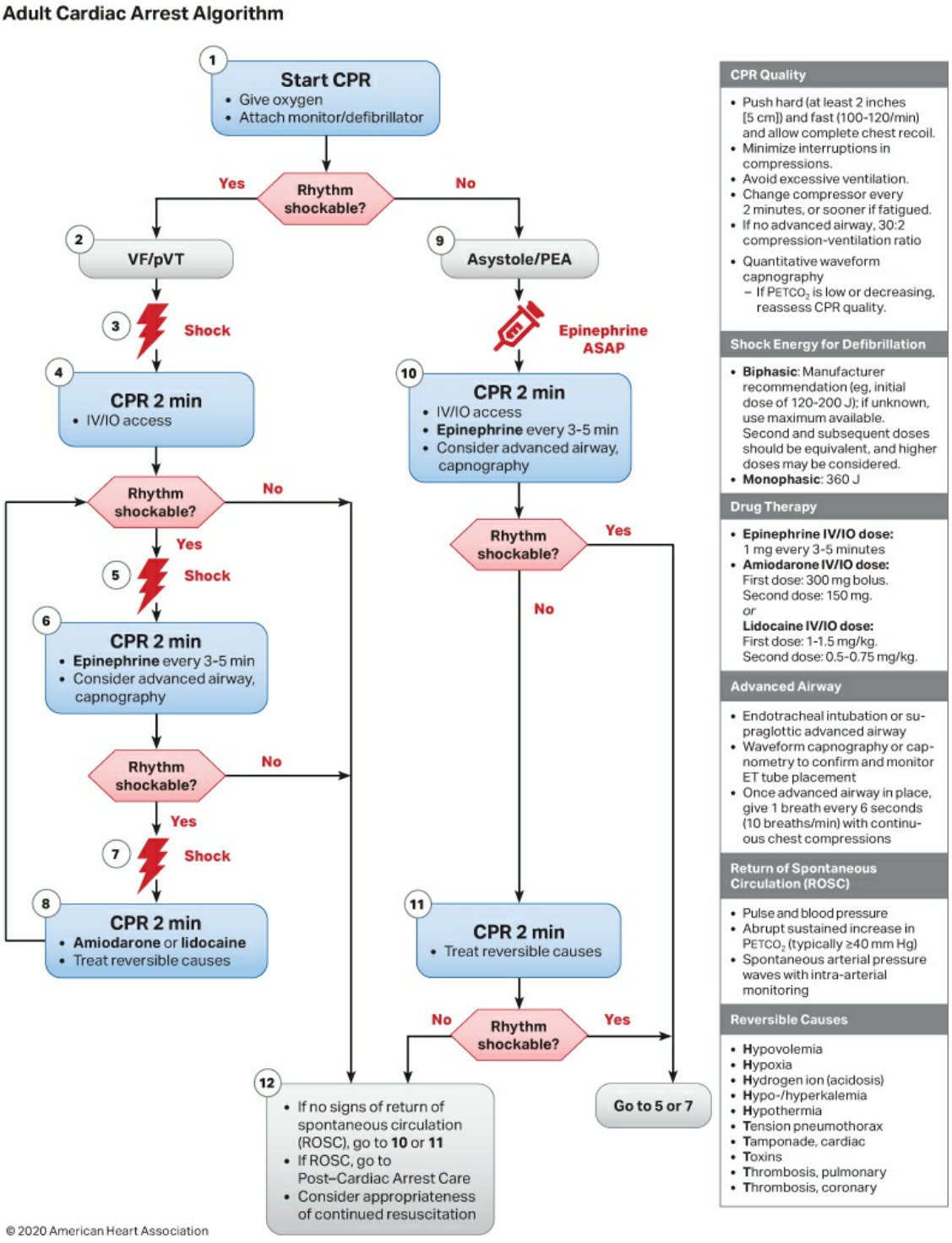

FIGURE 21.2 The American Heart Association algorithm for ACLS. Reprinted with permission Circulation. 2020; 142:S366–S468 © 2020 American Heart Association, Inc.

Actions

The benefit derived from epinephrine is the systemic vasoconstriction, which can increase flow in both the cerebral and coronary circulations. The increase in coronary blood flow is due to an increase in coronary perfusion pressure (the difference between aortic and right atrial pressures

between chest compressions). This is demonstrated in Figure 21.3 (20). In this case, there is a 30% increase in coronary perfusion pressure following IV epinephrine, and the effect lasts at least 3 minutes (the recommended time interval between epinephrine doses).

The disadvantage with epinephrine is the β-receptor-mediated cardiac stimulation, which can erase the benefit of increased coronary perfusion, and has also been implicated in post-resuscitation heart failure (20).

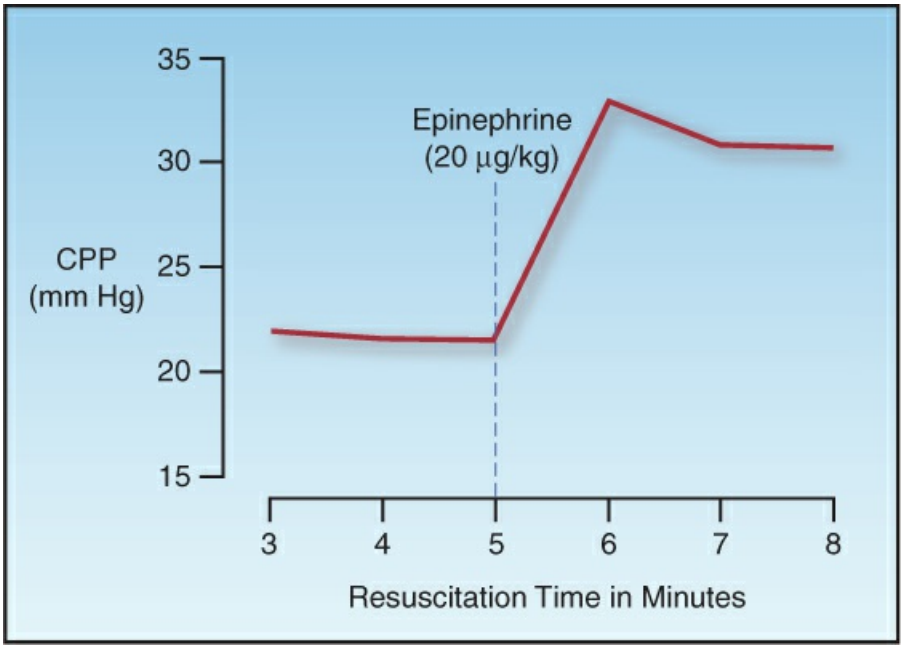

FIGURE 21.3 The effect of intravenous epinephrine on coronary perfusion pressure (CPP) during resuscitation of cardiac arrest with VF/pulseless VT. Data from Reference 15.

RESUSCITATION MONITORING

Monitoring for the return of spontaneous circulation (ROSC) has traditionally been limited to manual palpation for pulses, but this practice has a low sensitivity (21), and often requires interruption of chest compressions for extended periods of time (22). Ultrasound for carotid artery pulsations can speed the process of pulse detection (23), but also requires interruption of chest compressions. The end-tidal PCO_2 provides a more reliable (and physiological) evaluation of the circulation, and can be used to predict the likelihood of ROSC.

End-Tidal PCO_2

(The end-tidal PCO_2 measurement is described in detail in Chapter 7: see Figure 7.6.) The PCO_2 in exhaled gas at the end of expiration (end-tidal PCO_2) is a relection of the balance between ventilation and perfusion in the lungs. The end-tidal PCO_2 ($ETCO_2$) varies directly with changes in cardiac output relative to ventilation; i.e., *when alveolar ventilation is constant, changes in end-tidal PCO_2 reflect proportional changes in cardiac output* (e.g., a 30% decrease in end-tidal PCO_2 indicates a 30% decrease in the cardiac output). The baseline end-tidal PCO_2 is normally

equivalent to the arterial PCO_2 (i.e., about 40 mm Hg), but it is lower than the arterial PCO_2 in pulmonary conditions associated with increased physiologic dead space (i.e., V/Q ratio >1), such as chronic obstructive lung disease.

Using the End-Tidal PCO_2

The $ETCO_2$ has been suggested for monitoring the quality of chest compressions; i.e., an increase in depth of compressions is accompanied by an increase in $ETCO_2$ (24). More importantly, serial measurements of $ETCO_2$ during CPR can be used to identify the likelihood of the return of spontaneous circulation (ROSC). This is demonstrated by the graph in Figure 21.4, which show the serial changes in $ETCO_2$ during CPR in relation to ROSC (25). Patients who achieved ROSC showed a progressive increase in $ETCO_2$ during the 20-minute resuscitation period, whereas patients who did not achieve ROSC showed a progressive decline in $ETCO_2$. The $ETCO_2$ that separated responders from nonresponders in this study was 15 mm Hg after 20 minutes. Other studies have shown a discriminant $ETCO_2$ of 10 mm Hg for separating responders from nonresponders (26,27).

The sum of the evidence indicates that *a successful resuscitation is unlikely if the end tidal PCO_2 is not higher than 10–15 mm Hg after 20 minutes of CPR*. When the end-tidal PCO_2 remains above this level, continued resuscitation for as long as 1½ hours has been associated with a favorable outcome (28).

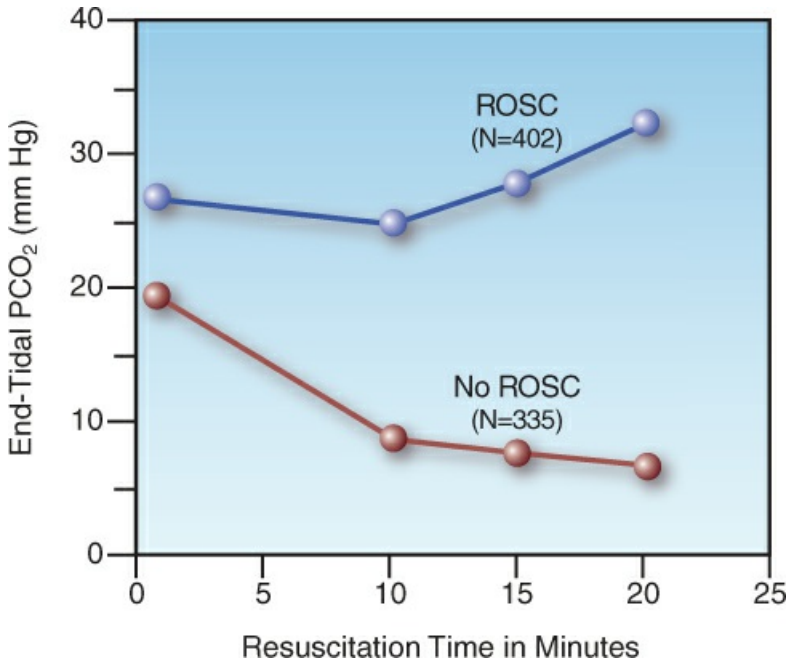

FIGURE 21.4 Serial changes in end tidal PCO_2 during CPR in relation to return of spontaneous circulation (ROSC) in 737 cases of out-of-hospital cardiac arrest. N indicates the number of patients in each group, and data points represent mean values. From Reference 25.

Ultrasound

Point-of-care ultrasound is invaluable for the detection of potentially reversible causes of cardiac

arrest, such as tension pneumothorax or pericardial tamponade. Ultrasound has a high sensitivity (91%) and specificity (99%) for the detection of pneumothoraces in the supine position (29), and pericardial effusions are readily detected in the subcostal or parasternal long-axis views (see Figure 21.5) (30). The traditional signs of pericardial tamponade (i.e., diastolic collapse of the right ventricle) are unreliable during a cardiac arrest (due to low intracardiac pressures), so the presence of any pericardial effusion should prompt immediate pericardiocentesis.

Studies in trauma-associated cardiac arrest have shown that ultrasound evidence of cardiac standstill is 100% predictive of failure to survive (31). However, there is considerable disagreement in the recognition of cardiac standstill among physicians that perform point-of-care ultrasound (32); as a result, the clinical practice guidelines for cardiac arrest do not recommend the ultrasound detection of cardiac standstill as a reason to terminate CPR (4).

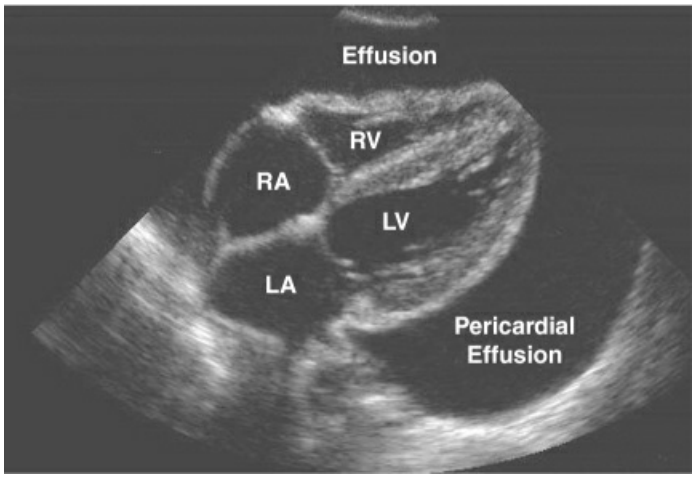

FIGURE 21.5 Ultrasound image (subcostal view) showing a large pericardial effusion, which appears as a broad anechoic band surrounding the heart. Image retouched from Loyola University Stritch School of Medicine, medical education curriculum in radiology, at www.stritch.luc.edu, accessed 11/18/2023.

POST-RESUSCITATION PERIOD

The immediate goal of CPR is a return of spontaneous circulation, but this does not ensure a satisfactory outcome. In fact, *about 70% of patients who survive the resuscitation do not survive the hospitalization* (33). This section describes the common problems encountered in the days following a successful resuscitation of cardiac arrest.

Post-Cardiac Arrest Syndrome

The return of spontaneous circulation is often followed by dysfunction in one or more major organs that can be progressive and ultimately fatal. This *post-cardiac arrest syndrome* is attributed to a combination of ischemic injury inflicted during the arrest, and a *reperfusion injury* from toxic substances released from ischemic tissues when blood flow is re-established (33,34). The principal features of this syndrome are summarized below:

. *Brain injury* is the most common manifestation of the post-cardiac arrest syndrome, and is *responsible for 23% to 68% of deaths following cardiac arrest* (33). Clinical manifestations

include failure to awaken, myoclonus, and generalized seizures. The high prevalence of brain injury after cardiac arrest is attributed to a limited tolerance to ischemia, and a predisposition to oxidative reperfusion injury from reactive oxygen species (34).

. Post-arrest *cardiac dysfunction* is a combination of systolic and diastolic dysfunction that can progress to cardiogenic shock within hours after ROSC (33). The underlying problem is a type of reperfusion injury known as myocardial "stunning", which usually resolves within 72 hours (33).

. A systemic inflammatory response (i.e., fever, leukocytosis, etc.) is almost universal after cardiac arrest, and can result in widespread inflammatory injury with multiorgan failure and circulatory shock. (See Chapter 17 for more on inflammatory shock.)

Targeted Temperature Management

Increased body temperature is well-known for its ability to aggravate ischemic brain injury (35), and control of body temperature has been a major focus of efforts to limit neurologic injury in patients who survive a cardiac arrest.

A Brief History

Induced hypothermia (originally called *human refrigeration*) was introduced for the management of post-cardiac arrest victims in the 1950s (36), but was abandoned because of the risks associated with hypothermia. About a half century later (in 2002), two studies were published showing that mild hypothermia (32–34° C) improved the chances of neurologic recovery in survivors of cardiac arrest who remained comatose (37,38). This led to the immediate adoption of induced hypothermia at 32–34° C for comatose survivors of cardiac arrest. About 10 years later, a large multicenter study showed that a target temperature of 36° C was equivalent to 33° C for influencing outcomes (39), and also reduced the risk of hemodynamic compromise (40). After another 10 years, the same group of investigators showed that a target temperature of 37.5° C (normothermia) was equivalent to 33° C for influencing outcomes (41). This brings us to the current state of affairs, where *the goal of targeted temperature management is to prevent fever in comatose survivors of cardiac arrest.*

TABLE 21.3 Targeted Temperature Management

Feature	Recommendations†
Indication	Patients who do not regain consciousness after ROSC
Goal	Body Temp ≤37.5° C (≤99.5° F) for 72 hours
Monitoring	Continuous monitoring of core body temperature; e.g., with a thermistor-equipped bladder catheter
Treatment Plan	1. Patients with mild hypothermia (32°–36° C) after ROSC should not be actively rewarmed. 2. Maintain body temp at ≤37.5° C with acetaminophen and reduced room temp, if needed. 3. If body temp rises above 37.7° C (>99.9° F), start active cooling, and set target temp at 37.5° C (99.5° F). 4. Surface cooling is acceptable. 5. Body temp is kept at ≤37.5° C for 72 hours, unless the patient awakens.

†From the clinical practice guidelines in Reference 3.

The Method

The salient features of targeted temperature management (TTM) are outlined in Table 21.3 (3,41). Candidates for TTM include all patients who do not regain consciousness after return of spontaneous circulation (ROSC), and the goal is to maintain a body temperature ≤37.5° C (99.5° F) for 72 hours after ROSC, or until the patient awakens. Continuous monitoring of core body temperature is required, and is easily accomplished with thermistor-equipped bladder catheters. A temperature-controlled cooling device is used only if the body temperature rises above 37.7° C (99.9° F), and if this occurs, surface cooling should be adequate, with the target temperature set at 37.5° C.

Despite the recommendation for normothermic TTM in the most recent clinical practice guidelines (3), there is a reluctance to abandon hypothermic TTM, and the option to use a target temperature of 33° C is left unresolved. However, the induction of hypothermia introduces a number of undesirable factors, such as the risk of hypotension (from cold-induced diuresis and cardiac depression), bradycardia (common during hypothermia), and shivering, which often requires heavy sedation (which can delay the assessment of mental status) and occasionally requires neuromuscular paralysis (which is never desirable).

Other Concerns

In addition to preventing fever, there are other concerns for the management of patients in the early post-arrest period. These are summarized in Table 21.4.

TABLE 21.4 Other Concerns in Post-Arrest Management

Intervention	Comment
Oxygen Inhalation	Hyperoxia aggravates neurologic injury after cardiac arrest, so O_2 inhalation should be used only to correct hypoxemia (SaO_2 <90%).
Vasopressor R_x	Maintaining a mean arterial pressure higher than usual (e.g., ≥75 mm Hg) may benefit neurologic recovery.
Vasopressor Agent	Norepinephrine is preferred to epinephrine (see text for explanation).
Glycemic Control	Hyperglycemia aggravates neurologic injury after cardiac arrest, but avoid very tight glycemic control because hypoglycemia also aggravates neurologic injury.

Oxygen Inhalation

Hyperoxia can aggravate the neurologic injury following cardiac arrest (42), and oxygen inhalation should be used only to correct hypoxemia (arterial O_2 saturation <90%) (6). Reactive oxygen species are implicated in the reperfusion injury that follows return of spontaneous circulation (34), which provides another reason to limit O_2 breathing in the post-arrest period.

Managing Hypotension

Ischemic brain injury is associated with dysfunctional autoregulation of cerebral blood flow; in

this situation, cerebral blood flow is dependent on the arterial blood pressure. As a result, hypotension (which is common after return of spontaneous circulation) can aggravate post-arrest brain injury, and should be treated aggressively. However, the optimal pressure in the post-arrest period is unclear. Although the standard recommendation for hypotension is to maintain a mean arterial pressure (MAP) ≥65 mm Hg (see Chapter 14), observational studies show that patients with higher blood pressures in the early post-arrest period have better neurologic outcomes (43,44). Therefore, targeting an MAP that is higher than usual (e.g., ≥75 mm Hg is a reasonable consideration in the early hours following return of spontaneous circulation.

VASOPRESSOR AGENT: There is a tendency to continue using epinephrine as a vasopressor for the hypotension that follows return of spontaneous circulation, but there is evidence that norepinephrine is associated with fewer cardiovascular deaths and improved neurologic outcomes when compared to epinephrine (45).

Glycemic Control

Hyperglycemia in the early post-arrest period is associated with a poor neurologic outcome (46), so attention to glycemic control is advised. However, strict glycemic control in critically ill patients is associated with frequent episodes of hypoglycemia (47), which also promotes neurologic injury, so a higher-than-normal *range of 145–180 mg/dL* for blood glucose is considered a reasonable target of glycemic control following cardiac arrest (48). As an adjunct to this practice, it seems wise to *avoid dextrose-containing intravenous solutions* whenever possible.

Predicting Neurologic Recovery

In patients who do not regain consciousness after return of spontaneous circulation (ROSC) or targeted temperature management, the single most important determination is the likelihood of neurologic recovery. The following is a description of what is involved in this determination. The predictors of a poor outcome with a high degree of certainty (i.e., few or no false positive results) are shown in Table 21.5. (A poor outcome is defined as death, persistent coma or vegetative state, or severe disability.)

TABLE 21.5 Predictors of a Poor Neurologic Outcome with a High Degree of Certainty

1. Absence of pupillary light reflexes bilaterally on day 4 after ROSC.
2. Absence of corneal reflexes bilaterally on day 4 after ROSC.
3. Absence of oculocephalic or gag reflexes on day 2 after ROSC.
4. Myoclonic status at any time after ROSC.
5. Bilateral absence of the N20 peak on somatosensory evoked potentials.
6. An EEG that shows nonconvulsive status epilepticus or background suppression with periodic discharges.

7. A CT scan that shows diffuse cerebral edema.

From Reference 51.

Time to Awaken

Most (80–95%) patients who regain consciousness after ROSC are awake after 72 hours (49), but it can take 5 days or even longer for all patients to awaken, especially patients subjected to induced hypothermia (i.e., target temps of 32–34° C) (50). In general, the time to awaken can be a poor predictor of neurologic outcome in the first week following CPR, especially in patients who are heavily sedated in the early period following ROSC.

Clinical Examination

The only findings on clinical examination that are highly predictive of a poor outcome are the absence of brainstem reflexes. The ones that predict a poor outcome with a high degree of certainty include the absence of pupillary light reflexes bilaterally or corneal reflexes bilaterally on day 4 after ROSC, and the absence of gag or oculocephalic reflexes on day 2 after ROSC (51). Contrary to popular perception, an abnormal extensor response to pain (i.e., decerebrate posturing) is not highly predictive of a poor neurological recovery (51).

Myoclonus

The appearance of myoclonus (sudden, brief, involuntary jerks) early after ROSC is an unfavorable sign, but it does not eliminate the possibility of a neurologic recovery. However, the appearance of myoclonic status epilepticus at any time after ROSC predicts a poor outcome with almost 100% certainty (51).

Evoked Potentials

Somatosensory evoked potentials are averaged responses in the central nervous system to peripheral nerve stimulation, and are measured at the skin surface (like an EEG). Bilateral absence of the N20 peak (from the somatosensory cortex) with median nerve stimulation is highly predictive of a poor outcome (51).

Electroencephalography

The following findings on an electroencephalogram (EEG) are highly predictive of a poor neurologic outcome: 1) an isoelectric EEG (i.e., all activity <2 μV); 2) the presence of nonconvulsive status epilepticus, and 3) background suppression with superimposed periodic discharges (51).

Imaging

Computed tomography of the brain can reveal a massive stroke or intracerebral hemorrhage with herniation, both indicating very poor prognosis. CT evidence of diffuse cerebral edema is also highly predictive of a poor outcome, especially if present on day 2 or later after the cardiac arrest (51).

A FINAL WORD

Perception vs. Reality

Cardiopulmonary resuscitation has always enjoyed a popularity far greater than deserved. This is evident in surveys of the general public, where 95% of respondents have unrealistic expectations about CPR (52), including the belief that more than half of cardiac arrest victims survive and return to daily life with no residual effects (53). Television shows fuel this perception, where CPR is portrayed as a success in up to 75% of cases (54).

The reality of CPR is far removed from the public perception, as shown in Table 21.1, which indicates that CPR has a successful outcome in only 1–7% of cases.

Why is this so important? Because patients decide whether CPR is performed, so faulty perception, not reality, is dictating the delivery of CPR.

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A Final Word

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Section VIII

RESPIRATORY DISORDERS

Respiration is thus a process of combustion, in truth very slow, but otherwise exactly like that of charcoal.

Antoine Lavoisier

Chapter 22

Acute Pulmonary Embolism

Doubt is not a pleasant condition, but certainty is absurd.

Voltaire

Venous thromboembolism (i.e., deep vein thrombosis and pulmonary embolism) is cited as the third leading cause of cardiovascular deaths worldwide (behind myocardial infarction and stroke) (1), and has an annual risk of almost 10% in adults over the age of 45 (2). There is a heightened risk of VTE in ICU patients, which mandates the preventive measures for VTE described in Chapter 5. This chapter focuses on the condition that is responsible for the life-threatening potential of VTE; i.e., acute pulmonary embolism.

There are two features of pulmonary embolism that deserve emphasis at the outset. First, pulmonary embolism is more common than suspected; e.g., autopsy studies in hospitalized patients report the presence pulmonary emboli in as many as 30% of patients (3), and in most of these cases, the condition was not suspected prior to death. Second, the clinical suspicion of pulmonary embolism is confirmed by diagnostic testing in as few as 10% of cases (4). These observations indicate that *pulmonary embolism suffers from both underdiagnosis and excessive diagnostic testing* (a rather unique pairing). This conundrum is adequately summarized in the following statement:

> The one certainty surrounding the issue of thromboembolism diagnosis in critically ill patients is that considerable uncertainty remains (5).

The emphasis in this chapter is on acute pulmonary embolism that requires admission to an ICU, or develops during the ICU stay. Many of the recommendations in the chapter are based on clinical practice guidelines, which are listed in the bibliography at the end of the chapter (6–9).

CLINICAL EVALUATION

The diagnostic problems mentioned in the introduction are explained by the clinical manifestations of acute pulmonary embolism, which are neither sensitive nor specific (see next).

Clinical Presentation

The typical presentation of acute pulmonary embolism (acute PE) is a patient with dyspnea, tachycardia, and hypoxemia, but these are signs of cardiopulmonary disease, and do not implicate an acute PE. The common manifestations of acute PE are listed in Table 22.1, along with the predictive value of each for the likelihood of disease (10). Note that none of the findings provides more than a 50% chance of identifying an acute PE (i.e., the positive predictive value), and that the absence of these findings does not exclude an acute PE (i.e., a negative predictive value of ≥98% is used to exclude the presence of a condition). Of particular interest is the negative predictive value of 70% for hypoxemia, which means that *30% of patients with an acute PE have a normal arterial PO_2*. The alveolar–arterial PO_2 (A-a PO_2) gradient can also be normal in acute PE (11).

TABLE 22.1 Predictive Findings of Clinical Value in Acute Pulmonary Embolism

Findings	Positive Predictive Value†	Negative Predictive Value‡
Dyspnea	37%	75%
Tachycardia	47%	86%
Tachypnea	48%	75%
Pleuritic chest pain	39%	71%
Hemoptysis	32%	67%
Pulmonary Infiltrate	33%	71%
Pleural Effusion	40%	69%
Hypoxemia	34%	70%

†Positive predictive value is the percentage of patients with the finding who have a pulmonary embolus.

‡Negative predictive value is the percentage of patients without the finding who do not have a pulmonary embolus.

From Reference 10.

Less common manifestations of acute PE include fever (15% of cases), which is usually below 102° F (12), and syncope (10% of cases), which is often associated with right heart strain (13). However, neither of these manifestations is specific for acute PE. Also worthy of mention, acute PE can be the cause of an acute exacerbation of COPD in a small percentage (<10%) of cases (14).

Predisposing Factors

Because the clinical manifestations of acute PE are non-specific, the presence or absence of predisposing factors for venous thrombosis is used to determine the probability that an acute PE is present (and hence the need for diagnostic testing). These predisposing factors are presented in Chapter 5, and will not be repeated here. However, all patients who spend more than a few days in the ICU should be considered at-risk for venous thrombosis (and hence acute PE), and this risk is especially high in postoperative patients and those with spinal cord injuries or multisystem trauma.

D-Dimer Assay

Active thrombosis is accompanied by some degree of clot lysis, and this produces cross-linked fibrin monomers, also called fibrin D-dimers, or simply *D-dimers*. Plasma D-dimer levels are elevated in the presence of acute thrombosis, and the D-dimer assay has become a popular tool for determining the probability of an acute PE.

Predictive Value

D-dimer levels have a positive predictive value of 27%, and a negative predictive value of 92% (15), which means that an elevated D-dimer level does not indicate a high probability of acute PE, but a normal D-dimer level is evidence against the presence of acute PE (and venous thrombosis). There are several conditions other than thrombosis that elevate D-dimer levels, including sepsis, inflammatory conditions, heart failure, renal failure, pregnancy, and advanced age (15). This would explain why a majority (up to 80%) of ICU patients have elevated plasma D-dimer levels (16), and for this reason, the D-dimer assay is not considered a useful diagnostic test in the ICU setting.

Summary

There are no clinical or laboratory findings that predict the presence of a pulmonary emboli with certainty, and the suspicion of acute PE is usually based on the presence of predisposing factors, and the absence of evidence for other conditions that could be responsible for the clinical presentation. Unfortunately, this is a flawed practice, since pulmonary emboli are found in as few as 10% of the diagnostic imaging studies obtained for suspected PE (4).

DIAGNOSTIC IMAGING

The imaging methods in Table 22.2 are used to confirm or exclude the diagnosis of acute PE. The following is a brief description of each method.

TABLE 22.2 Diagnostic Imaging Studies for Acute Pulmonary Embolism

Study	Features
Venous Ultrasound	Positive: Reveals proximal leg DVT in 30–50% of cases of acute PE, which eliminates the need for other diagnostic tests. Negative: A negative result does not eliminate the possibility of acute PE.
CT Pulmonary Angiography (CTPA)	Positive: The method of choice for the detection of pulmonary emboli. Negative: The risk of contrast-induced nephropathy limits use when CrCL <30 mL/min/1.73 m^2. Radiation dose is also relatively high[1], which raises concerns about its use in pregnancy and breast feeding.
Ventilation-Perfusion Lung Scan	Positive: No radiocontrast dye, and has a lower radiation dose than CTPA[1]. Negative: Diagnostic yield is limited in the presence of pulmonary infiltrates or chronic lung disease.

Echocardiography	Positive: Can be diagnostic for acute PE (i.e., mobile right-sided thrombi or McConnell's sign). Negative: Diagnostic findings are infrequent.

[1]See text for radiation dose.

Venous Ultrasound

Most pulmonary emboli originate from deep venous thrombosis (DVT) in the thigh and groin (6), so the evaluation of suspected PE can begin with a bedside ultrasound examination of the proximal leg veins. Venous ultrasound is advantageous in patients who are not suitable candidates for the other imaging methods (see later), and it is appealing in ICU patients because it eliminates the risk associated with transport to the radiology suite.

Methodology

Venous ultrasound is described in Chapter 1. There are two methods for identifying venous thrombosis. The principal method is *compression ultrasound*, where a compressive force is applied to a vein that is situated under the ultrasound probe. This normally compresses the vein and obliterates the lumen, (see Figure 1.7), but veins that are filled with thrombi will not compress. Therefore, an incompressible vein is used as evidence of venous thrombosis (17).

The *color Doppler mode* of ultrasound can be used as an adjunct to venous compression. This method converts flow velocities into color images, and the flow in arteries and veins can be identified by the direction of flow in relation to the ultrasound probe (see Figure 1.8). Venous thrombosis is then characterized by sluggish or absent flow in an incompressible vein. The combination of compression and color Doppler ultrasound is known as *duplex ultrasound*.

Test Performance

For the detection of proximal DVT in the legs, duplex ultrasound has a sensitivity ≥95%, a specificity ≥97%, a positive predictive value of 97%, and a negative predictive value of 98% (17). These numbers indicate that duplex ultrasound is a reliable method for the detection of proximal DVT in the legs.

Clinical studies have shown that 30–50% of patients with acute PE will have ultrasound evidence of proximal DVT in the legs (6,18). When DVT is detected by ultrasound, no further workup for pulmonary emboli is necessary (unless the patient is hemodynamically unstable), and anticoagulation is started using the same regimens used for acute PE. (Anticoagulation for DVT and PE differs only in the duration of treatment.) When venous ultrasound is unrevealing, another diagnostic imaging test is required.

Upper Extremity DVT

Thrombosis in the axillary and subclavian veins can develop as a result of indwelling central venous catheters. Upper extremity DVT does not frequently result in symptomatic acute PE (<10% of cases) (19), but inspection for swelling of the upper arms is warranted in patients with indwelling central venous catheters. Venous ultrasound is reliable for the detection of upper extremity DVT, with a sensitivity of 97% and a specificity of 96% (19). A positive study warrants anticoagulation and immediate removal of the responsible catheter (Table 22.2.).

CT Pulmonary Angiography

The diagnostic test of choice for acute PE is computed tomographic pulmonary angiography (CTPA) (6–9), which has replaced conventional pulmonary angiography. This is a specialized method of CT that uses a spiral or helical scanner that rotates around the patient to produce a "volumetric" two-dimensional view of the lungs. When multidetector scanners are used, peripheral injection of a radiocontrast agent allows visualization of the pulmonary arteries down to the subsegmental level. Pulmonary emboli appear as filling defects, as shown in Figure 22.1.

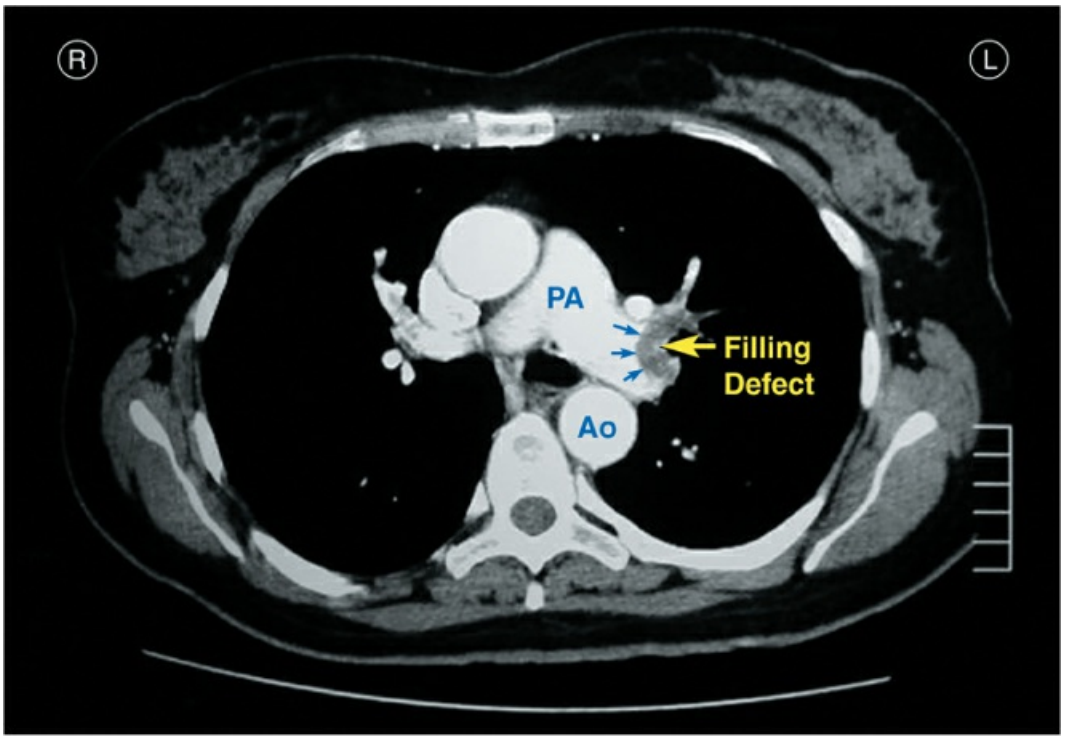

FIGURE 22.1 CT pulmonary angiogram showing a pulmonary embolus, which appears as a filling defect in the left main pulmonary artery. AO = aorta, PA = pulmonary artery. Image digitally retouched

Multidetector CTPA has a negative predictive value of 95% (20), which means a normal CTPA essentially eliminates the possibility of acute PE.

Subsegmental Emboli

The detection of pulmonary emboli on CTPA usually prompts immediate anticoagulant therapy, but there is some evidence that small emboli in subsegmental arteries (<2.5 mm in diameter) may not require anticoagulation. An analysis of the pooled results of 14 clinical studies showed that withholding anticoagulation in patients with subsegmental emboli and no evidence of DVT had no significant influence on mortality rate or recurrence rate for PE (21). However, a more recent study showed that withholding anticoagulation was not detrimental if there was a single subsegmental embolus, but if there were multiple subsegmental emboli, the recurrence rate for PE was much higher without anticoagulation (22).

WHAT TO DO: Based on the available studies, it seems reasonable to withhold anticoagulation for

subsegmental pulmonary emboli if the following conditions are satisfied: 1) there is a single subsegmental embolus, 2) there is no residual clot burden in the legs (by venous ultrasound), 3) there is no evidence of RV dysfunction, and 4) there are no significant co-morbidities (e.g., hypoxemia).

Adverse Effects

The major concern with CTPA is the risk of nephrotoxicity from the radiocontrast dye. Predisposing factors include renal insufficiency, diabetes, and volume depletion. The current recommendation is to avoid radiocontrast dye, if possible, when renal function is unstable, or the creatinine clearance is <30 mL/min/1.73 m^2 (23). If CTPA is considered necessary, protection from dye-induced nephropathy is possible with a regimen of volume infusion and intravenous N-acetylcysteine (24). (See Chapter 34 for more on dye-induced nephropathy.) CTPA is also contraindicated in patients with a history of dye-induced anaphylaxis.

RADIATION EXPOSURE: An undesirable feature of CTPA that is often overlooked is the relatively high radiation exposure, which averages 15 millisieverts (mSv) per procedure (25). To place this in perspective, the average radiation exposure from a chest x-ray (single view) is 0.02 mSv (25), and the annual radiation limit for workers is 50 mSv (26). Because of the radiation dose, alternatives to CTPA should be considered during pregnancy and breast feeding (6). (Appendix 2 contains a table that lists the radiation dose of common radiographic procedures.)

Lung Scintigraphy

Radionuclide ventilation-perfusion scans (V/Q scans) were popular prior to the introduction of CT pulmonary angiography. However, they are no longer favored because the presence of lung disease (particularly infiltrative disease) produces abnormal scans. As a result, V/Q scans have diagnostic value in only 20–30% of cases (27). They are most reliable in younger patients with no underlying lung disease (which excludes most ICU patients, and have a much lower radiation exposure (~2 mSv) than CTPA studies.

The major role of V/Q scans is in cases of suspected PE where CT angiography is not performed (e.g., because of renal failure or a history of dye-induced anaphylaxis). V/Q scans have three possible results (6):

. A normal V/Q scan has no ventilation or perfusion defects, and excludes the diagnosis of acute PE.

. A high probability V/Q scan has perfusion defects without associated ventilation defects, and confirms the diagnosis of acute PE.

. An indeterminate V/Q scan has matching ventilation and perfusion defects, and can neither exclude nor confirm the diagnosis of acute PE.

About three-quarters of V/Q scans are indeterminate, which has no diagnostic value, but the combination of an indeterminate scan and a negative venous ultrasound study can be used to exclude the diagnosis of acute PE, but only in patients who are hemodynamically stable (6).

Echocardiography

Transthoracic echocardiography is typically obtained after the diagnosis of acute PE has been confirmed, to look for signs of right ventricular (RV) dysfunction (see Figure 18.2). Evidence of right heart strain (i.e., RV dilation with elevated troponin levels) has prognostic significance in acute PE, but has no diagnostic significance (i.e., is not specific for PE).

Diagnostic Aids

There are two findings on transthoracic cardiac ultrasound that are specific for acute PE:

. Mobile thrombi in the right heart have been reported in 2–18% of patients with acute PE (28,29), and are more prevalent in cases of massive PE (28).

. Akinesis of the free wall of the RV, combined with normal motion at the apex (called McConnell's sign) is considered specific for acute PE (30), and is reported in 20% of cases (28).

These two findings are relatively infrequent, but they add diagnostic value to cardiac ultrasound in cases where the other imaging modalities are nondiagnostic.

MANAGEMENT

The early management of acute PE is organized according to a risk stratification system (based on the risk of an unfavorable outcome) that has three levels of illness severity:

. Low-risk PE: No right ventricular dysfunction, hemodynamic instability, or significant co-morbid conditions (e.g., hypoxemia).

. Intermediate-risk PE: (Also known as submassive PE) Evidence of right ventricular dysfunction (with or without elevated troponin levels), but no hemodynamic instability.

. High-risk PE: (Also known as massive PE.) Evidence of right heart strain (RV dysfunction plus elevated troponin levels) with hemodynamic instability.

The antithrombotic strategies for each risk level are summarized in Table 22.3.

TABLE 22.3 Antinthrombotic Strategies for Acute Pulmonary Embolism

Risk Category	Recommendations
Low Risk	1. Start oral anticoagulation with either: a. Apixaban: 10 mg BID x 7 days, then 5 mg BID. b. Rivaroxaban: 15 mg BID x 3 weeks, then 20 mg once daily. 2. If CrCL ≤30 mL/min/1.73 m^2, use warfarin, and anticoagulate with reduced-dose enoxaparin (1 mg/kg once daily) until the INR is therapeutic.
Intermediate Risk	1. Start anticoagulation with enoxaparin (1 mg/kg subQ every 12 hrs). 2. If no deterioration after 24–48 hrs, switch to an oral anticoagulant using the recommendations for low-risk PE.
High Risk	1. Start anticoagulation with unfractionated heparin, using the weight-based regimen below: a. Give IV load of 80 IU/kg. then infuse at 18 U/kg/hr.

	b. Check PTT at 6 hrs, and adjust dose to a target PTT of 46–70 sec. 2. Initiate thrombolytic therapy as soon as possible (if no contraindications). The recommended drug regimens are: a. Alteplase (tPA): 100 mg infused over 2 hrs. b. For impending cardiovascular collapse, give 0.6 mg/kg over 15 minutes (max = 50 mg). 3. If the condition does not improve, consider catheter-directed thrombolysis or embolectomy.

Low-Risk PE

Oral anticoagulation (started as soon as possible after the diagnosis) is suitable for low-risk PE, and the direct-acting oral anticoagulants DOACs) are preferred to warfarin for reasons explained in Chapter 19. The drug regimens with documented success in treating venous thromboembolism are *rivaroxaban* in a dose of 15 mg twice daily for 3 weeks, then 20 mg once daily (31) and *apixaban* in a dose of 10 mg twice daily for 7 days, then 5 mg twice daily (32). The starting dose for both of these drugs is higher than usual (see Table 19.3), but there is no increase in the risk of bleeding.

DOACs are not recommended when renal function is impaired and the creatinine clearance is ≤30 mL/min/1.73 m^2 (6). (*Note:* 1.73 m^2 is the body surface area of an average-sized adult.) In this situation, warfarin is the recommended oral anticoagulant. However, at least 2–3 days are required to achieve therapeutic anticoagulation after starting warfarin, and reduced-dose enoxaparin (i.e., 1 mg/kg once daily) is recommended for maintaining anticoagulation until the INR reaches the therapeutic range (6). Enoxaparin can be used down to a CrCL of 15 mL/min (33).

Finally, since oral anticoagulants are used for low-risk PE, and the drug effect is not monitored, patients can be discharged (from the emergency department or the hospital) if there are no significant co-morbidities (e.g., hypoxemia).

Intermediate-Risk PE

Because patients with intermediate-risk PE have some degree of RV dysfunction, and may have right heart strain (i.e., RV dysfunction plus elevated troponins) (34), they are monitored in the hospital for 24–48 hours for signs of hemodynamic deterioration. During this time, enoxaparin is recommended for anticoagulation (6), using a dose of 1 mg/kg every 12 hours. If there is no deterioration after the observation period, oral anticoagulation can be started, using the drugs and dosing regimens recommended for low-risk PE.

Thrombolytic Therapy

Thrombolytic therapy is not officially recommended for intermediate-risk PE, but it has been used (by this author and others) in cases of severe RV dysfunction or unresolving right-heart strain (i.e., RV dysfunction plus elevated troponin levels). Studies in patients with PE and right heart strain have shown that thrombolytic therapy reduces the risk of cardiovascular decompensation, but is also increases the risk of serious bleeding, including intracranial hemorrhage (see later). The risk of bleeding, more than lack of a hemodynamic benefit, has discouraged the use of thrombolytic therapy in hemodynamically stable cases of PE.

High-Risk RE

High-risk PE is a life-threatening condition, with severe RV dysfunction leading to

hemodynamic instability. The principal goals of management are reperfusion of the pulmonary circulation and hemodynamic improvement.

Anticoagulation

Unfractionated heparin (UFH) is recommended for early anticoagulation in high-risk patients using the weight-based dosing regimen in Table 22.3 (which uses actual body weight) 6). Weight-based dosing achieves more rapid anticoagulation than fixed dosing (35). As always with unfractionated heparin, therapy is aimed at achieving an activated partial thromboplastin time (PTT) of 46–70 seconds, or 1.5 to 2.5 times control. (Most ICUs have a heparin dosing guideline.) Heparin is continued through thrombolytic therapy until the condition improves or stabilizes.

HEPARIN DOSING IN OBESITY: The popular weight-based dosing regimen for heparin was derived in patients weighing less than 130 kg (286 lbs). For body weights in excess of 130 kg, this regimen will overestimate the heparin dose and promote excessive anticoagulation (36). To avoid this problem, the adjusted body weight shown here is recommended for weight-based heparin dosing in patients with morbid obesity (i.e., a body mass index ≥40 kg/m^2) (37).

$$\text{Adjusted Weight (kg)} = \text{IBW} + 0.4 \times (\text{actual} - \text{ideal body weight}) \qquad (22.1)$$

where IBW = ideal body weight. (Appendix 2 has a table of ideal body weights in adults). The adjusted body weight is almost halfway between the ideal and actual body weights.

Thrombolytic Therapy

Thrombolytic therapy is recommended for all patients with high-risk PE and hemodynamic instability. Absolute contraindications to thrombolytic therapy include active bleeding, a prior hemorrhagic stroke, an ischemic stroke within the past 6 months, central nervous system neoplasm, and major trauma, surgery, or head injury in the past 3 weeks (6).

DRUG REGIMEN: The recommended drug regimen is alteplase (tPA), 100 mg infused over 2 hours, and an accelerated regimen (0.6 mg/kg over 15 minutes to a maximum dose of 50 mg) is recommended if there is impending (or actual) cardiovascular collapse (6).

Heparin is used in conjunction with thrombolytic therapy, and the infusion can be continued during the thrombolytic treatment period (although it is frequently stopped and restarted after the fibrinolytic agent is given). Heparin therapy is particularly advantageous after thrombolysis because clot dissolution releases thrombin, and this can promote thrombotic reocclusion of the involved vessel.

SYSTEMIC VS. DIRECTED THROMBOLYSIS: Traditional (systemic) thrombolytic therapy provides some hemodynamic benefit (e.g., a decrease in pulmonary artery pressures), but there is a 10–12% incidence of major bleeding (including intracranial hemorrhage in 1–2% of cases) (38,39), and this erases the overall benefit of the treatment. Catheter-directed thrombolysis (through a catheter placed in the pulmonary artery) uses a lower thrombolytic dose, and causes fewer major bleeding episodes than systemic thrombolysis (40). (The effects on pulmonary artery pressures are similar to systemic thrombolytic therapy.) The major shortcoming of catheter-directed

thrombolysis is availability (an interventional radiologist is needed to place the catheter under fluoroscopic guidance), especially since the benefit of thrombolytic therapy is time-dependent; i.e., the greatest benefit occurs within 48 hours of symptom onset (6).

Mechanical Thrombectomy

Clot removal from the pulmonary arteries is possible using specialized catheters that are inserted percutaneously into the femoral vein and advanced into the pulmonary arteries. The emboli are located by contrast injection, and are then removed by aspiration. The clot burden that can be removed with this procedure is shown in Figure 22.2.

Mechanical thrombectomy can result in dramatic improvements in pulmonary artery pressures and RV function (much greater than seen with thrombolytic therapy), and these changes persist for at least three months after the procedure (41). Although it is currently recommended as a rescue procedure when thrombolytic therapy fails or is contraindicated (6), it could be used as a replacement for thrombolytic therapy, if available. In fact, a look at the amount of clot removed from the pulmonary arteries in Figure 22.2 provides an explanation of why thrombolytic therapy has had such a limited impact in life-threatening pulmonary embolism.

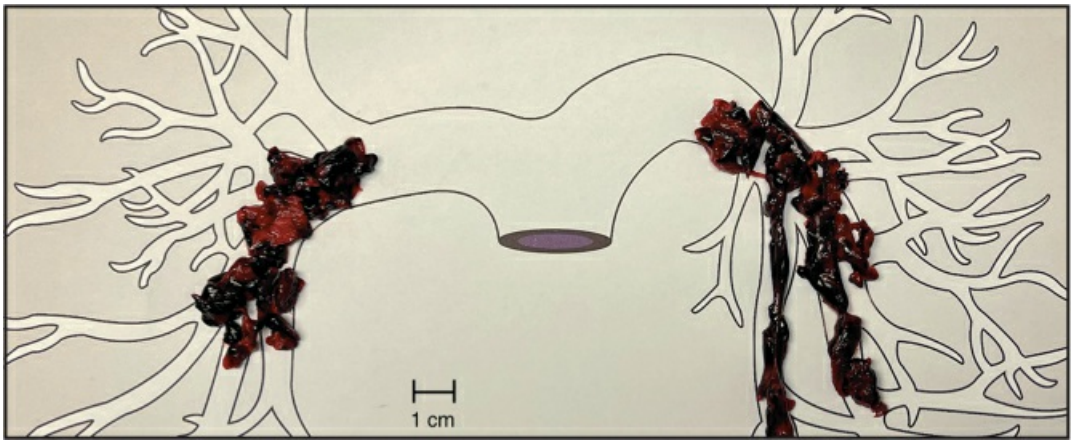

FIGURE 22.2 Catheter-based clot retrieval from the pulmonary arteries in a patient with acute pulmonary embolism and severe right heart strain. Image courtesy of Dr. Brian Shaw, DO (digitally retouched).

Hemodynamic Management

The management of cardiovascular compromise from an acute PE is challenging, because the primary problem is a physical obstruction in the pulmonary arteries. The following are some relevant points about management:

. Aggressive volume infusion can be detrimental in acute PE because it can increase volume overload in the right ventricle, which will push the interventricular septum into the left ventricle and impede left ventricular filling (see Figure 18.2). Because of this risk, cardiac ultrasound should be used to guide fluid management in acute PE.

. In the setting of right heart failure, a normal central venous pressure (4–6 mm Hg) can be used as evidence of hypovolemia (and the subsequent need for volume infusion). However, the volume infused should be limited to 500 mL (6), because of the previously mentioned risk. Once again, cardiac ultrasound should be used to guide volume infusion.

. Current guidelines recommend dobutamine as a consideration when there is right heart strain and the blood pressure is normal (i.e., intermediate-risk PE) (6). Dobutamine is a vasodilator, and should not be used alone if acute PE results in hypotension. (See Table 16.3 for the dobutamine dosing regimen.)

. Norepinephrine is recommended for hypotension in acute PE because it does not increase pulmonary vascular resistance (6).

Vena Cava Filters

The aim of anticoagulation in acute PE is not to dissolve the existing embolus, but to prevent the next one. When anticoagulation is not possible, or is not effective, meshlike filters can be placed in the inferior vena cava (IVC) to prevent recurrent PEs from leg veins (42).

Filter Design

Inferior vena cava (IVC) filters have progressed through several iterations. The earliest filters were shaped like an umbrella, and were problematic because as they filled with trapped blood clots, they would obstruct the IVC and create troublesome leg edema. The design that led to the popularity of IVC filters is shown in Figure 22.3. The design benefit is an elongated, conical shape (like a badminton birdie), which allows the basket to fill to 75% of its capacity without compromising the cross-sectional area of the vena cava. This limits the risk of vena cava obstruction and leg edema.

IVC filters are inserted percutaneously into the internal jugular vein or femoral vein, and are placed below the renal veins, if possible. The early filters (like the one in Figure 22.3) were permanent, but retrievable filters were introduced in 2003 (43), and the most recent iteration is a biodegradable filter with a basket that dissolves after 60 days (44).

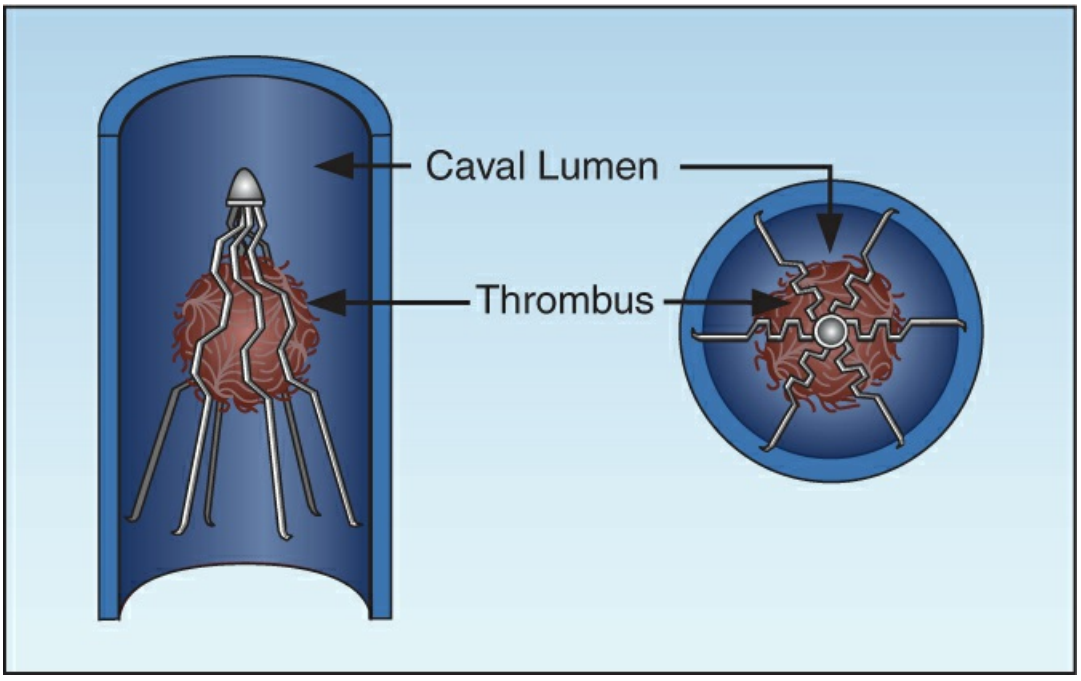

FIGURE 22.3 The Greenfield™ vena cava filter (Boston Scientific, Malborough, MA). The elongated, conical shape allows the basket to trap blood clots without obstructing blood flow,

and the struts have hooked ends to anchor the filter to the wall of the vena cava.

Indications

The consensus indications for placement of an IVC filter are as follows:

. The presence of a DVT or acute PE and an absolute contraindication to anticoagulation (e.g., from active bleeding).

. An acute PE that occurs while receiving therapeutic doses of an anticoagulant, and the likely source is DVT in the legs or pelvis (and not in an upper extremity).

IVC filters are also used as a preventive measure in conditions with a high risk of venous thromboembolism, such as multisystem trauma or bariatric surgery. Clinical studies have shown that the prophylactic use of IVC filters reduces the risk of acute PE by about 60%, but there is also a 70% increase in the incidence of DVT (45), so the overall benefit of the practice is questioned (6).

The Clinical Experience

Although not devoid of risk, IVC filters are remarkably safe and effective. The incidence of symptomatic PE after filter placement is about 5% (46), and life-threatening complications (e.g., migration of the filter) are reported in less than 1% of cases (46). One of the intriguing features of IVC filters (and one that is rarely mentioned) is that they never seem to get infected, even when exposed to bacteremia.

A FINAL WORD

An Exercise in Diagnostic Uncertainty

The experience with venous thromboembolism, which is far from satisfying, can be summarized as follows:

. When you think it's there, it usually isn't; i.e., when a pulmonary embolism is suspected, the diagnosis is confirmed in as few as 10% of cases.

. When it is there, you usually don't know it; i.e., in most cases of pulmonary embolism, the source of the embolus is clinically silent.

. The best thing to do, then, is to prevent it (as described in Chapter 5).

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Chapter 23

Asthma and COPD in the ICU

Asthmatic distress calls for procedures which stimulate the sympathetic and dilate the bronchi.

Lawrason Brown, MD (*a*)

Admission to an ICU is an ominous sign for patients with acute exacerbations of asthma and chronic obstructive pulmonary disease (COPD). For COPD patients, one of every four will not survive the hospitalization, and 40% of the survivors will be readmitted within a year (1). And for patients with asthma, the need for mechanical ventilation has been identified as the strongest risk factor for death (2).

This chapter describes the management of acute exacerbations of asthma and COPD, including some relevant issues related to positive pressure ventilation in patients with severe airflow obstructions. As customary, the recommendations in this chapter will follow the most recent clinical practice guidelines, which are listed in the bibliography at the end of the chapter (3–6).

One point of interest deserves mention before proceeding. The management of asthma and COPD is centered on dilating the airways with adrenergic agents, which is very similar to the statement in the introductory quote. The interesting point is that this statement was made almost 100 years ago, in 1931 (*a*). The significance of this is left to the judgment of the reader.

BASICS

Monitoring Airway Obstruction

The management of obstructive airways disease is guided by the severity of obstruction in the airways.

Clinical Evaluation

During acute exacerbations of asthma or COPD, *the clinical examination is often unreliable for determining the severity of airway obstruction* (7). There are usually signs of respiratory distress, including tachycardia, tachypnea, use of accessory muscles of respiration, and inability to

complete sentences without taking a breath, and there may be altered mentation and pulsus paradoxus (i.e., an inspiratory drop in systolic pressure >12 mm Hg). However, none of these clinical findings is sensitive or specific for severe airways obstruction, and more objective measures are recommended (3).

Measures of Peak Expiratory Flow

For spontaneously breathing patients, a readily obtainable bedside measure of airway obstruction is the peak expiratory flow rate (PEFR) (3). The PEFR varies with age, gender, and height, and measurements are typically expressed as "% predicted" (observed result/predicted result × 100), with the predicted values derived from standard reference equations. (Appendix 2 contains tables of the predicted PEFR for age, gender, and height.) The correlations between the % predicted values and the severity of airway obstruction are shown below (3).

% Predicted PEFR	Severity of Obstruction
≥70%	Mild
40–69%	Moderate
<40%	Severe

In general, a PEFR <200 L/min indicates severe airways obstruction, and hypercapnia does not occur until the PEFR falls below 25% of predicted (8).

LIMITATION: The PEFR is effort-dependent, and accurate measurements requires a maximum inspiratory effort (to total lung capacity) followed by a maximum expiratory effort (to residual lung volume). Patients with acute exacerbations of asthma and COPD are typically unable to perform these maneuvers because of respiratory distress, and monitoring PEFR has not been popular in the acute care setting (9). However, after the respiratory distress subsides, periodic measurements of the PEFR can be used to monitor the course of the illness.

Intrinsic PEEP

One of the consequences of severe airflow obstruction is the inability to fully exhale the volume of air that is inhaled. The retained volume causes hyperinflation of the lungs and a positive pressure in the alveoli at the end of expiration. This positive end-expiratory pressure (PEEP), which is called *intrinsic PEEP*, is a reflection of the severity of airflow obstruction, and it can be monitored during mechanical ventilation. Intrinsic PEEP is described in more detail later in the chapter.

Aerosol Drug Delivery

Aerosolized bronchodilators are the backbone of management for obstructive airways disease, and there are three devices used to generate these aerosols: the *nebulizer*, the *metered-dose inhaler*, and the *dry powder inhaler*. There are three types of nebulizers (jet, mesh, and ultrasonic nebulizers), but the description here is limited to the jet nebulizer (the traditional device). The design of a jet nebulizer and a metered dose inhaler is shown in Figure 23.1. (*Note:* Dry powder inhalers are rarely used for life-threatening airways obstruction, and are not described here.)

Jet Nebulizer

The pneumatic or jet nebulizer uses the same principle as an air-entrainment mask. A high-pressure gas source (e.g., 50 psi from a wall outlet) is passed through a narrow opening in the nebulizer, creating a high-velocity (jet) stream of gas that is passed over the opening of a narrow tube submerged in a drug solution. The gas jet draws the drug solution up the tube (by creating viscous drag) and then pulverizes the solution to create an aerosol spray that is inhaled by the patient. Small-volume jet nebulizers have a reservoir volume of 3–6 mL, and can completely aerosolize the reservoir volume in less than 10 minutes (10). Large-volume nebulizers have a reservoir volume >200 mL, and are used for continuous aerosol therapy (see later).

LUNG DEPOSITION: Although small-volume nebulizers can completely aerosolize a drug solution, only a fraction of the drug aerosol reaches the lungs. This is demonstrated in Table 23.1, which shows the distribution of aerosolized albuterol with different aerosol generator systems (11). When the nebulizer is used, most of the drug aerosol impacts on the delivery apparatus or is exhaled, and only 12% of the intended dose reaches the lungs. Inefficient drug delivery is characteristic of aerosol drug therapy, and is not specific for the jet nebulizer.

TABLE 23.1 Distribution of Aerosolized Albuterol by Delivery System

Site of Deposition	Nebulizer (2.5 mg)	MDI (200 µg)	MDI + Spacer (200 µg)
Exhaled Gas	20%	1%	1%
Apparatus	66%	10%	78%
Oropharynx	2%	80%	1%
Lungs	12%	9%	20%

From Reference 11. MDI = metered dose inhaler. The MDI dose of 200 µg is equivalent to 2 puffs.

Metered Dose Inhaler

A metered dose inhaler (MDI) operates like a canister of hair spray. The MDI has a pressurized canister that contains a drug solution with a boiling point below room temperature. When the canister is squeezed between the thumb and fingers, a valve opens that releases a fixed volume of the drug solution. The liquid immediately vaporizes when it emerges from the canister, and a liquid propellant in the solution creates a high velocity spray.

LUNG DEPOSITION: The spray generated by an MDI has a velocity in excess of 30 meters per second (over 60 miles per hour) (12), and when delivered directly into the mouth, most of the spray impacts on the posterior wall of the oropharynx (called “inertial impaction”), and is not inhaled. The data in Table 23.1 shows that 80% of the aerosolized drug is deposited in the oropharynx, and only 9% reaches the lungs. Drug deposition in the lungs can be increased by adding a holding chamber or “spacer” between the MDI and the mouth, which reduces the spray velocity. This is confirmed by the data in Table 23.1, which shows a more than two-fold increase in the inhaled drug spray when a spacer was used with the MDI. *Spacers are recommended for all bronchodilator treatments that use MDIs* (10).

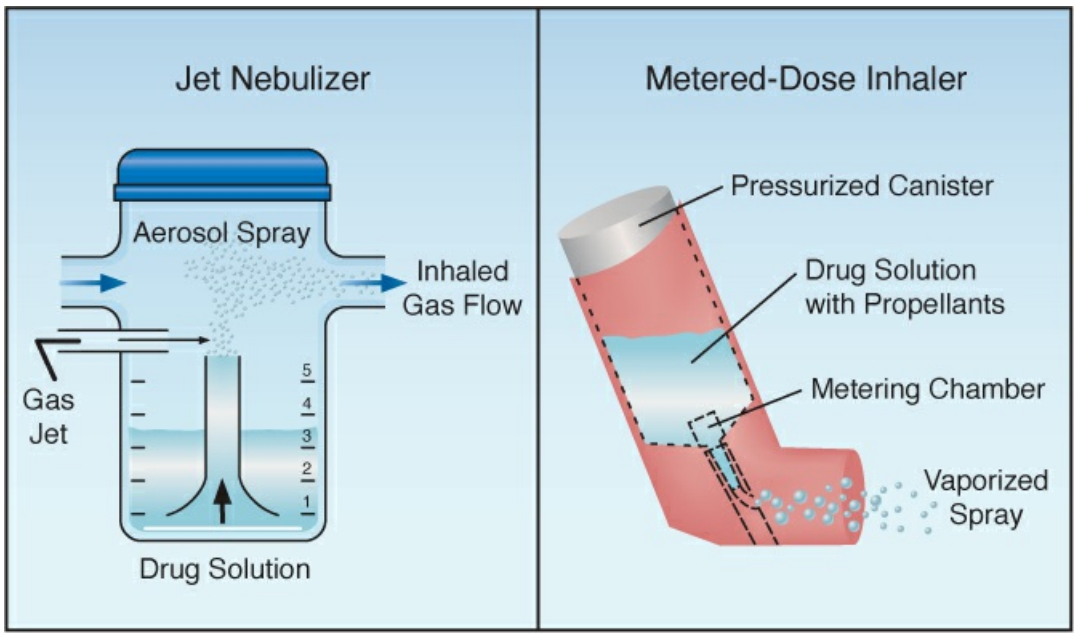

FIGURE 23.1 Aerosol generators used to deliver bronchodilator drugs by inhalation. See text for explanation.

Nebulizer vs. Metered-Dose Inhaler

Bronchodilator treatments with nebulizers and MDIs produce equivalent results despite a marked difference in drug dosage. This is demonstrated in Figure 23.2 which shows a comparison of the bronchodilator responses to three treatments with albuterol given by nebulizer or MDI (with spacer) in patients with acute exacerbation of asthma (13). Note the similarity in bronchodilator responses with nebulizers and MDIs, despite a 7-fold difference between the nebulizer dose (2.5 mg) and the MDI dose (0.36 mg, or 4 puffs). Adjusting for the inhaled dose (from the percentages in Table 23.1) yields an albuterol dose of 12% of 2.5 mg (300 μg) for the nebulizer, and 20% of 0.36 mg (72 μg) for the MDI, which is a 4-fold difference in the inhaled drug dosage. This dose-response discrepancy is unexplained.

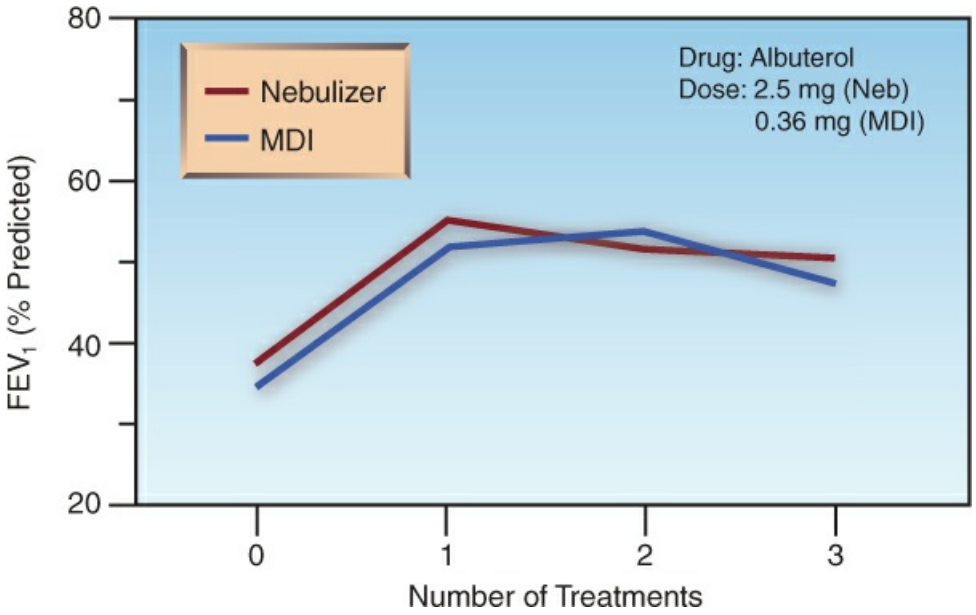

FIGURE 23.2 Comparison of the bronchodilator response to albuterol given by nebulizer or metered-dose inhaler (MDI) in patients with acute exacerbation of asthma. Three treatments were given at 30-minute intervals, using doses indicated in the upper right portion of the graph. FEV_1 = forced expiratory volume in one second. Data from Reference 16.

Mechanical Ventilation

During mechanical ventilation, aerosolized albuterol is delivered through the inspiratory arm of the ventilator tubing using a nebulizer or MDI with spacer. Unfortunately, aerosol deposition in the lungs is impaired further during mechanical ventilation, thanks to condensation on the ventilator tubing and endotracheal tube (14). Aerosol deposition in the lungs can be enhanced by decreasing the inspiratory flow rate and increasing the duration of inspiration (15).

Despite less aerosol deposition in the lungs during mechanical ventilation, the dose of aerosolized albuterol is the same for spontaneous breathing patients and during mechanical ventilation (see later for the doses). And once again, there is no difference in bronchodilator responses with nebulizers or MDIs (16).

Which Method is Preferred?

MDIs (with spacers) are generally preferred because of the lower drug dose, which minimizes side effects. Some people have difficulty coordinating their breathing with drug release from the MDI, but the introduction of breath-actuated MDIs should eliminate this problem. Nebulizers are preferred for acute exacerbations of asthma and COPD, but a switch to MDIs is initiated when the condition stabilizes

ACUTE EXACERBATION OF ASTHMA

The flow diagram in Figure 23.3 summarizes the early management of adults with acute exacerbation of asthma, and is from the National Asthma Education Program (1). This protocol is based on objective measures of airway obstruction (e.g., peak expiratory flow rate), but clinical measures of disease severity (e.g., tachycardia, use of accessory muscles, etc.) are also

suitable (17,18). Note that a normal arterial PCO_2 ($PaCO_2$ = 42 mm Hg) despite bronchodilator treatments warrants admission to the ICU. This is explained by the minute ventilation, which is increased (often doubled) in acute asthma, and would normally result in a decrease in $PaCO_2$ Therefore, a normal $PaCO_2$ in the face of a high minute ventilation represents CO_2 retention, and is a sign of severe airway obstruction.

The following is a description of the recommended drugs and dosing regimens for acute exacerbations of asthma. These are summarized in Table 23.2

Short-Acting β_2-Agonists

The favored bronchodilators are drugs that stimulate β_2 receptors in bronchial smooth muscle, and aerosol delivery is preferred because it is more effective than oral (19) or intravenous (20) drug delivery, and has fewer side effects. Short-acting β_2-agonists (SABAs) are preferred for acute exacerbations of asthma, while long-acting β-agents are favored for maintenance therapy.

Albuterol is the most widely used SABA for acute exacerbations of asthma (3). Aerosolized albuterol has a rapid onset of action (less than 5 minutes), with a peak effect at 15–60 minutes, and a duration of 2–5 hours (21). *Levalbuterol* is the R-enantiomer of albuterol (a more active form of the drug) that is equally effective at half the dose. However, clinical studies have not shown an advantage with levalbuterol over albuterol (1,17).

Aerosol Regimens

The following regimens of aerosolized albuterol are recommended for acute exacerbations of asthma (3,17,18):

. The initial treatment involves up to three 20-minute treatments using 2.5 to 5 mg albuterol by nebulizer or 4–8 puffs (90 μg per puff) by MDI with a spacer. Nebulizer delivery is favored for patients with severe airflow obstruction (3), although there is no evidence that nebulizers produce better bronchodilator responses than MDIs (22).

. If further therapy is needed, albuterol can be given hourly for up to 3 hours, or can be given by continuous nebulization using doses of 5–15 mg/hr. Continuous aerosol therapy is popular, and may be more effective than intermittent aerosol therapy in patients with severe airflow obstruction (23).

. For patients who are admitted to the hospital, albuterol (2.5–5 mg by nebulizer or 4–8 puffs by MDI) is given every 4–6 hours for the duration of the hospital stay.

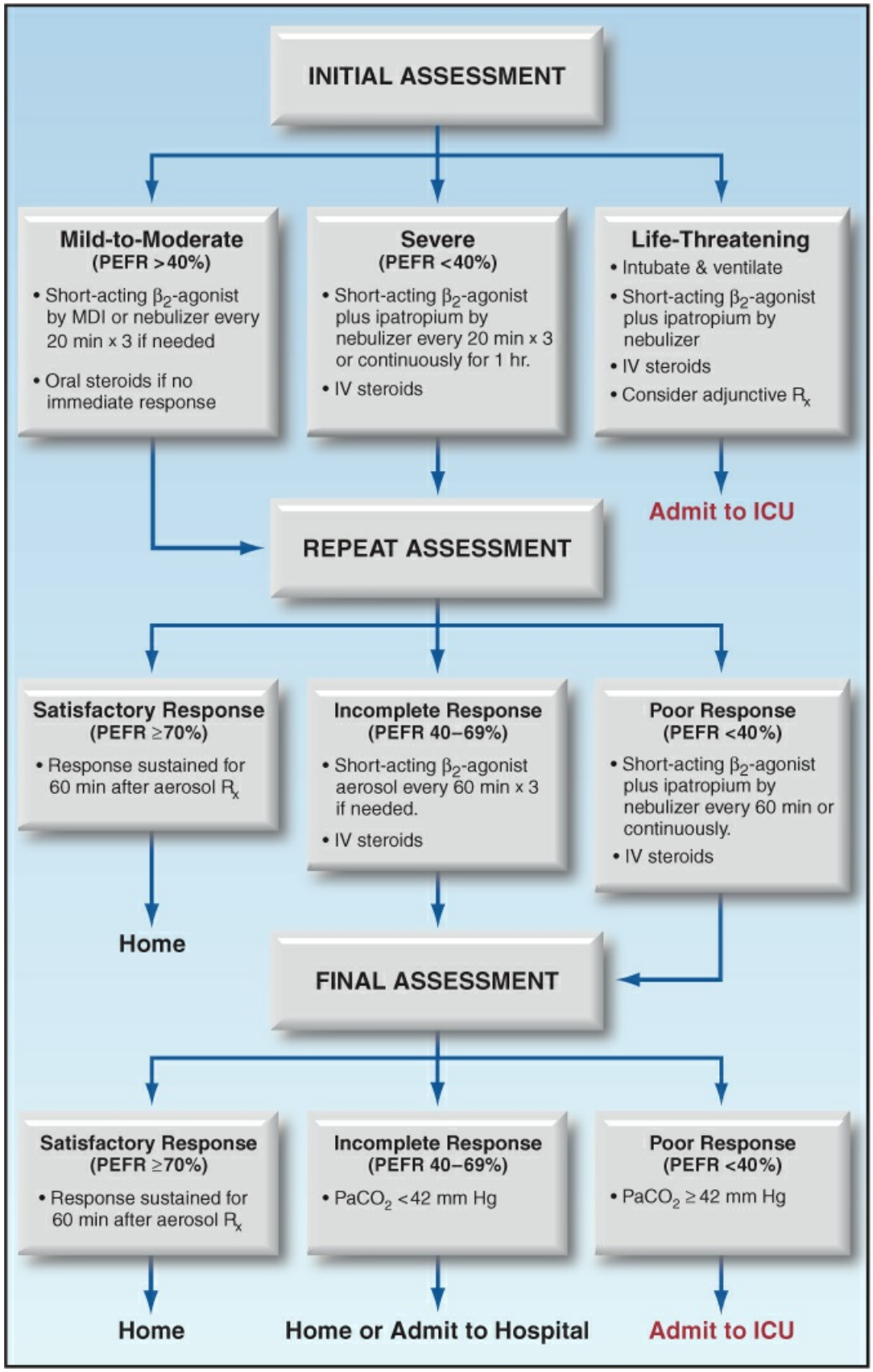
INITIAL ASSESSMENT
Mild-to-Moderate
(PEFR >40%)
• Short-acting β_2-agonist by MDI or nebulizer every 20 min x 3 if needed
• Oral steroids if no immediate response
Severe
(PEFR <40%)
• Short-acting β_2-agonist plus ipatropium by nebulizer every 20 min x 3 or continuously for 1 hr.
• IV steroids
Life-Threatening
• Intubate & ventilate
• Short-acting β_2-agonist plus ipatropium by nebulizer
• IV steroids
• Consider adjunctive R_x
Admit to ICU
REPEAT ASSESSMENT
Satisfactory Response
(PEFR ≥70%)
• Response sustained for 60 min after aerosol R_x
Incomplete Response
(PEFR 40–69%)
• Short-acting β_2-agonist aerosol every 60 min x 3 if needed.
• IV steroids
Poor Response
(PEFR <40%)
• Short-acting β_2-agonist plus ipatropium by nebulizer every 60 min or continuously.
• IV steroids
Home
FINAL ASSESSMENT
Satisfactory Response
(PEFR ≥70%)
• Response sustained for 60 min after aerosol R_x
Incomplete Response
(PEFR 40–69%)
• $PaCO_2$ <42 mm Hg
Poor Response
(PEFR <40%)
• $PaCO_2$ ≥42 mm Hg
Home
Home or Admit to Hospital
Admit to ICU

FIGURE 23.3 Flow diagram showing the early management of acute exacerbations of asthma, as recommended in the National Asthma Education Program (3). PEFR = peak expiratory flow rate.

Parenteral Therapy

For the rare asthmatic patient who does not tolerate bronchodilator aerosols (usually because of excessive coughing) parenteral therapy can be given using subcutaneous *epinephrine* (0.3 to 0.5 mg every 20 minutes for 3 doses) or subcutaneous *terbutaline* (0.25 mg every 20 minutes for 3 doses) (3).

Side Effects

Aggressive aerosol therapy with SABAs can produce a number of side effects, including tachycardia, tremors, hyperglycemia, hypokalemia, hypomagnesemia, hypophosphatemia, and elevated plasma lactate levels (24–26). The decrease in serum potassium is the result of a β-receptor-mediated shift of potassium into cells. The source of the elevated lactate levels is likely to be an increase in the metabolic rate, and not anaerobic metabolism (26).

TABLE 23.2 Drug Regimens for Acute Exacerbations of Asthma

Drug	Dosing Regimens
Albuterol	Dosing: 2.5–5 mg (or 4–8 puffs) every 20 min for 3 doses, then if needed, continue hourly doses, or start continuous inhalation at 5–15 mg/hr, for up to 3 hrs. Maintenance dose is 2.5 mg (or 2 puffs) every 4–6 hrs. Comment: Aggressive dosing can elevate lactate levels.
Levalbuterol	Dosing: 1.25–2.5 mg (or 4–8 puffs) every 20 min for 3 doses, then if needed, continue hourly doses for up to 3 hrs. Maintenance dose is 1.25 mg (or 2 puffs) every 4–6 hrs. Comment: No proven benefit over albuterol.
Ipratropium	Dosing: 0.5 mg every 20 min for 3 doses, then as needed. Can be added (0.5 mg/hr) to continuous inhalation of albuterol. Comment: Use only if initial response to albuterol is not satisfactory, but do not continue use after admission to hospital.
Corticosteroids	Dosing: 40–80 mg of prednisone (PO) or methylprednisolone (IV) initially, then continue daily, in 1 or 2 divided doses, for 7–10 days. Comment: Benefit is not immediate, and takes up to 12 hrs to develop. Taper not necessary after a 10-day course of therapy.
Magnesium	Dosing: 2 grams of $MgSO_4$ IV over 15–30 min. Comment: Use only if initial response to albuterol is not satisfactory.

Anticholinergic Agents

Anticholinergic agents offer only marginal benefits in acute asthma, and are used in combination with a SABAs for severe exacerbations, and only for the first 3–4 hours of therapy (3,27).

The only anticholinergic agent approved for use in asthma is *ipratropium bromide*, a derivative of atropine that blocks muscarinic receptors in the airways. The dose in acute asthma is 0.5 mg (which can be mixed with albuterol in the nebulizer) every 20 minutes for 3 doses, then

as needed, or 8 puffs (18 μg per puff) by MDI every 20 min as needed, for up to 3 hours (3). Systemic absorption is minimal, and there is little risk of anticholinergic side effects (e.g., tachycardia, dry mouth, blurred vision, urinary retention). Ipratropium has no proven benefit beyond the first few hours of management, and it *should be discontinued in patients who are admitted for continued asthma management* (3).

Corticosteroids

Corticosteroids are considered a staple in the management of both acute and chronic asthma because of their anti-inflammatory effects. Clinical studies have shown that corticosteroids can hasten the resolution of acute asthma and reduce the risk of relapses (28), although not all studies show a benefit from corticosteroids in acute asthma (29,30). The following observations about steroid therapy in asthma deserve mention:

. There is no difference in efficacy between oral and intravenous steroids (28,31).

. The beneficial effects of steroids are often not apparent until 12 hours after therapy is started (31), so steroid therapy will not influence the clinical course of asthma in the emergency department.

. There is no apparent dose-response curve for steroids (31), and no evidence that doses above 100 mg of prednisone daily (or equivalent doses of other steroids) provide added benefit in acute asthma (28).

. A 10-day course of steroids can be stopped abruptly without a tapering dose (28,32).

Regimen in Acute Asthma

The National Asthma Education Program includes the following recommendations for corticosteroid therapy in acute exacerbations of asthma (3).

. Steroids are recommended for all patients who do not show a satisfactory response after one or two bronchodilator treatments.

. Oral steroids are recommended for patients who can tolerate oral medications.

. The recommended dose is 40–80 mg daily of *prednisone* (for oral therapy) or *methylprednisolone* (for intravenous therapy) in one or two divided doses, which is continued until there is evidence of satisfactory resolution.

. Inhaled corticosteroids can be started at any time during treatment of an acute exacerbation of asthma, and are continued after systemic steroids are discontinued, to reduce the risk of relapses.

Mechanism of Action?

The beneficial effects of steroids in acute asthma are attributed to their anti-inflammatory actions. However, the comparative features of corticosteroids in Table 23.3 indicates that *dexamethasone is the most potent anti-inflammatory corticosteroid* (33), yet it is not recommended for the treatment of asthma. This raises questions about the actions of steroids in asthma (as well as the numerous other inflammatory conditions where steroids other than dexamethasone are recommended).

TABLE 23.3	Comparison of the Therapeutic Steroids		
Corticosteroid	**Equivalent Dose (mg)**	**Relative Anti-inflammatory Activity**	**Relative Mineralocorticoid Activity**
Hydrocortisone	20	1	20
Prednisone	5	3.50	1
Methylprednisolone	4	5	0.5
Dexamethasone	0.75	30–40	0

Adjunctive Measures

The following measures can be helpful when acute asthma does dot resolve after initial bronchodilator therapy.

Magnesium

Magnesium has mild bronchodilator effects (possibly as a result of calcium channel blockade), and intravenous magnesium (2 grams $MgSO_4$ infused over 15–30 minutes) can hasten the resolution of acute asthma when the response to albuterol, ipratropium, and steroids is not satisfactory (34). Clinical studies of inhaled magnesium (150 mg $MgSO_4$) have produced inconsistent results (35), and the inhaled route is not currently advised.

Ketamine

Sedation can be beneficial by reducing the respiratory rate, which will reduce the tendency for air trapping and hyperinflation of the lungs (see later for a description of air trapping). Sedation with ketamine also provides some bronchodilation, and there are several reports of ketamine facilitating the resolution of acute asthma in patients who were refractory to initial bronchodilatory therapy (36). The effective dose is 0.1–0.2 mg/kg IV as a loading dose, followed by a continuous infusion at 0.15–0.25 mg/kg/hr (for 1 to 5 hours) (36). Reported side effects include dysphoria, hallucinations, and increased secretions.

Oxygen Therapy

Hypoxemia is common in severe exacerbations of asthma, and supplemental O_2 should be used to maintain the arterial O_2 saturation (SaO_2) at ≥90%. Conventional O_2 delivery systems can provide O_2 at rates up to 15 L/min, but inspiratory flow rates in acute asthma can exceed 60 L/min, so a high-flow nasal O_2 system (which delivers heated and humidified O_2 at rates of 40–60 L/min) may be necessary to correct hypoxemia. (High-flow nasal O_2 systems are described in Chapter 25.)

Noninvasive Ventilation

The most severe cases of acute asthma are accompanied by hypercapnia, and these cases may require a trial of noninvasive ventilation with “bilevel positive airway pressure” (BiPAP), which is described in Chapter 26. Failure of BiPAP to lower the arterial PCO_2 is often an indication for

intubation and mechanical ventilation.

ACUTE EXACERBATION OF COPD

Acute exacerbations of COPD are most often the result of a respiratory infection, a covert pulmonary embolus, or left-sided heart failure (5); in some cases, a precipitating event is never identified. Exacerbations that warrant ICU admission are typically those with hypoxemic and hypercapnic respiratory failure, with progressive hypercapnia that may depress mentation.

The management of COPD exacerbations, other than treating any underlying cause, is centered on bronchodilators and corticosteroids, very much like the management of acute asthma. This is a curious approach, since *COPD is characterized by a lack of bronchodilator responsiveness on pulmonary function tests* (5).

Bronchodilator Therapy

The same bronchodilators used in acute asthma are recommended for acute exacerbations of COPD, but the dosing regimens differ, as shown in Table 23.4. Ipratropium is used as combination therapy when the response to short-acting β_2-agonists is less than satisfactory, although at least three clinical studies do not support this practice (37).

TABLE 23.4 Drug Regimens for Acute Exacerbations of COPD

Drug	Dosing Regimens
Albuterol	Dosing: 2.5–5 mg by nebulizer, or 2–8 puffs by MDI with spacer, every 4–6 hrs. Comment: MDI favored over nebulizer because of equivalent bronchodilator response at a much lower dose.
Levalbuterol	Dosing: 1.25–2.5 mg by nebulizer, or 2–8 puffs by MDI with spacer, every 4–6 hrs. Comment: More potent form of albuterol, but has no proven advantage.
Ipratropium	Dosing: 0.5 mg by nebulizer, or 2–8 puffs by MDI with spacer, every 4–6 hrs. Comment: Use as combination therapy only when response to short-acting β_2-agonists is less than satisfactory.
Corticosteroids	Dosing: 40 mg of prednisone-equivalents daily for 5 days. Comment: Oral therapy is equivalent to intravenous therapy.

Corticosteroids

Corticosteroid therapy is associated with a faster recovery and fewer treatment failures in acute exacerbations of COPD (5). *At least 9 patients must be treated with corticosteroids to avoid one treatment failure* (38), but on the other hand, *a steroid-related adverse event occurs once in every 6 patients treated* (38). However, since an adverse effect of steroids (e.g., hyperglycemia) is likely to be less troublesome than a treatment failure, the risk/benefit ratio is in favor of steroid therapy.

The recommended steroid regimen for COPD exacerbations is 40 mg prednisone (or equivalent doses of other steroids) daily for 5 days (5). The intravenous route offers no

advantage over the oral route (5,38,39).

Antibiotics

Airways infections are common triggers for COPD exacerbations, but only about 50% are caused by treatable bacterial infections (40), and this limits the benefit of antimicrobial therapy.

Indications

The most current clinical practice guidelines (5) recommend antibiotic therapy for the following conditions (other than pneumonias): an increase in sputum production, grossly purulent sputum, or the need for noninvasive or invasive mechanical ventilation. The latter conditions apply to most ICU admissions for exacerbations of COPD, so it is reasonable to assume that *all ICU admissions for acute exacerbations of COPD are candidates for antibiotic therapy*.

Empiric Treatment

Sputum cultures are problematic in COPD because the same organisms are often isolated during stable periods and in acute exacerbations (41). Common isolates include *Hemophilus influenzae* and *Streptococcus pneumoniae* (41), as well as gram-negative enteric organisms (e.g., *Pseudomonas aeruginosa*) in ventilator-dependent patients (42). Empiric coverage for both gram-positive and gram-negative pathogens (e.g., cefepime)seems wise for ICU patients, and the recommended duration of antibiotic coverage is 5–7 days (5).

Oxygen Therapy

In cases of severe COPD with chronic hypercapnia, high concentrations of inhaled O_2 can promote further increases in arterial PCO_2. This was originally attributed to loss of hypoxic ventilatory drive (43), but more recent studies have shown that the oxygen-induced rise in arterial PCO_2 is not accompanied by a decrease in ventilatory drive (44). Oxygen unloading of CO_2 from hemoglobin (i.e., the Haldane Effect) may play a role in this phenomenon. Regardless of the mechanism, it is important to avoid high concentrations of inhaled O_2 in patients with chronic CO_2 retention. The goal of oxygen therapy in COPD exacerbations is an arterial O_2 saturation (SaO_2) of 88–92% (and no higher) (5).

Noninvasive Ventilation

Exacerbations of COPD with troublesome hypercapnia should be managed initially with noninvasive ventilation using “bilevel positive airway pressure” (BiPAP) (45), which is described in Chapter 26. Failure of BiPAP to reduce the arterial PCO_2 by 10 mm Hg after one hour is an indication for intubation and mechanical ventilation (46).

POSITIVE-PRESSURE VENTILATION

Patients admitted to the ICU because of asthma or COPD often receive some form of positive-pressure ventilatory assistance (either noninvasive measures like BiPAP or conventional mechanical ventilation), and the following are some important considerations related to positive

pressure breathing in these patients.

Dynamic Hyperinflation

During spontaneous breathing in normal subjects, the volume of air (or gas) inhaled is completely exhaled before the end of expiration. In this situation, there is no expiratory airflow at the end of expiration, so the pressure in the distal airspaces is equivalent to atmospheric (zero reference) pressure. This is illustrated in the lower pressure-volume loop in Figure 23.4. In patients with severe airways obstruction from asthma or COPD, exhalation is prolonged, and is not completed before the next inhalation. This results in hyperinflation, called *dynamic hyperinflation*, and the trapped gas in the distal airspaces creates a positive end-expiratory pressure (PEEP), which is called *intrinsic PEEP* or *auto-PEEP* (47). This is illustrated by the upper pressure-volume loop on Figure 23.4. In this situation, breathing occurs on a flatter portion of the pressure volume curve, which means that the respiratory muscles must generate a higher transpulmonary pressure to draw a given volume of air into the lungs. This increases the work of breathing in patients with severe airflow obstruction. (If you want to feel what it is like to breathe in a hyperinflated state, take a deep breath, and try breathing from there.)

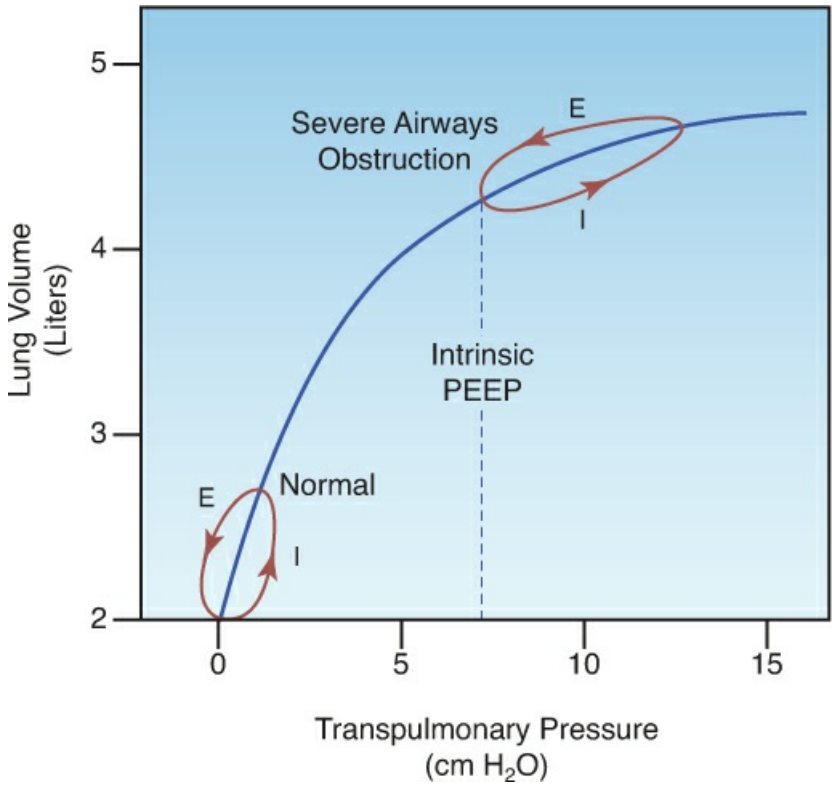

FIGURE 23.4 Pressure-volume curves showing the effects of severe airways obstruction on lung volumes and transpulmonary pressures. The hysteresis loops show the pressure and volume changes during inspiration (I) and expiration (E) for a single breath, See text for further explanation.

Positive Pressure Ventilation

The positive intrathoracic pressures created by positive-pressure ventilation will be increased in the presence of dynamic hyperinflation and intrinsic PEEP (because you are starting at a higher

pressure). In addition, positive-pressure ventilation can aggravate the hyperinflation (by delivering high inflation volumes or rapid rates) (48), and this will produce further increases in intrathoracic pressure. The elevated intrathoracic pressures can have two adverse consequences: (a) the increase in peak intrathoracic pressure promotes *barotrauma* (e.g., pneumothorax), and (b) the increase in mean intrathoracic pressure can impede venous return to the heart. The following measures can help to reduce the risk of these adverse consequences.

Monitoring

Dynamic hyperinflation can be detected by monitoring the flow waveforms during mechanical ventilation, as illustrated in Figure 23.5. The normal flow waveforms in the upper panel show that the expiratory flow ceases before the next lung inflation, while the flow waveforms in the lower panel show that expiratory flow is continuing when the next lung inflation is delivered. *The presence of expiratory flow at the end of expiration is evidence of dynamic hyperinflation.*

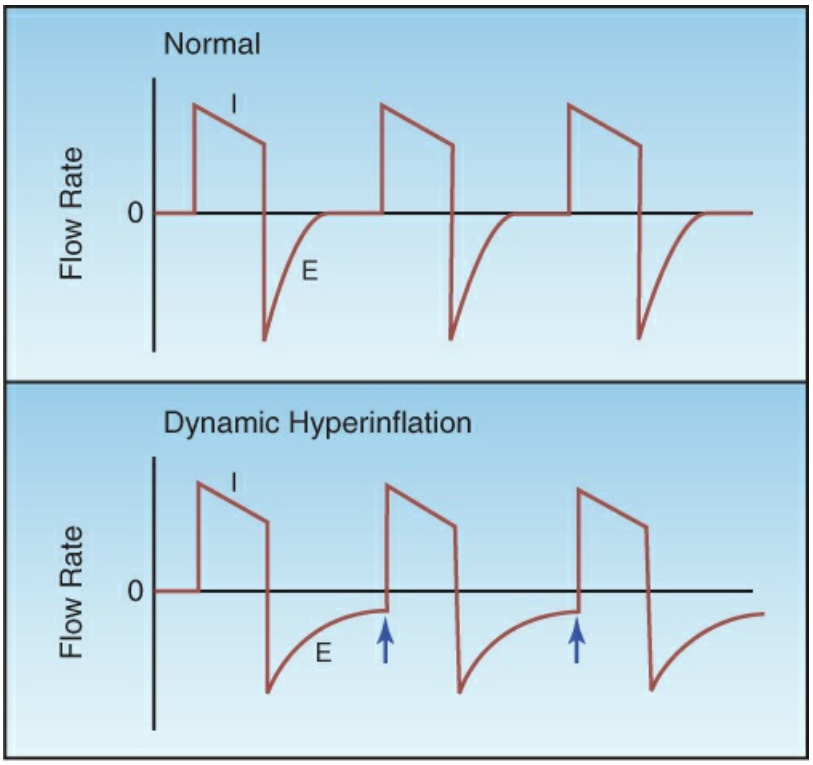

FIGURE 23.5 Flow waveforms during positive pressure mechanical ventilation. The waveforms in the lower panel show continuing expiratory flow at the end of expiration (indicated by the arrows), which indicates the presence of dynamic hyperinflation and intrisic PEEP. I = inspiration, E = expiration.

INTRINSIC PEEP: When there is evidence of dynamic hyperinflation on the flow waveforms, the severity of the problem can be evaluated by monitoring the level of intrinsic PEEP. (The measurement of intrinsic PEEP is described in Chapter 28.) *The intrinsic PEEP level is a reflection of the severity of airways obstruction in patients with asthma and COPD.*

Ventilator Strategies

The following adjustments are designed to limit dynamic hyperinflation (and the adverse consequences of high intrathoracic pressures) during mechanical ventilation:

. Avoid inflation volumes that exceed 6–8 mL/kg.

. Maximize the time allowed for exhalation by: (a) slowing a rapid breathing rate with sedation, if possible, and (b) increasing the inspiratory flow rate, if needed, so that lung inflation accounts for only one-third of the respiratory cycle.

The management of hyperinflation and intrinsic PEEP during mechanical ventilation is described further in Chapter 28.

A FINAL WORD

Keeping it Simple

The management of patients admitted to the ICU because of severe exacerbations of asthma or COPD can be summarized as follows:

. Give bronchodilators and corticosteroids to all patients, plus antibiotics for patients with severe COPD.

. If the condition is severe or progresses despite the above measures, use noninvasive ventilation if possible, and conventional mechanical ventilation if necessary.

That's about it.

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Chapter 24

Acute Respiratory Distress Syndrome

Physicians think they do a lot for a patient when they give his disease a name.

Immanuel Kant

The disease entity described in this chapter has had several names over the years, including shock lung, Da Nang lung (from the Vietnam war), stiff-lung, leaky capillary pulmonary edema, noncardiogenic pulmonary edema, acute lung injury, adult respiratory distress syndrome, and most recently, *acute respiratory distress syndrome*, or *ARDS*. However, none of these names provides any useful information about the disease, which is a diffuse inflammatory injury of the lungs, and one of the leading causes of acute respiratory failure in modern times (1–3).

PATHOGENESIS

The first clinical report of ARDS appeared in 1967 (4), and included 12 patients with refractory hypoxemia and bilateral, diffuse infiltrates on chest x-ray. Seven patients died, and autopsy findings revealed dense infiltration of the lungs with an inflammatory exudate. There was no evidence of infection, which indicated that ARDS is an acute inflammatory lung injury.

Inflammatory Injury

The lung consolidation in ARDS originates with the activation of circulating neutrophils (5). This leads to neutrophil sequestration in the pulmonary microcirculation, where the neutrophils attach to the vascular endothelium and move between endothelial cells and into the lung parenchyma. The neutrophils then degranulate to release the contents of their cytoplasmic granules (i.e., proteolytic enzymes and toxic oxygen metabolites). Subsequent damage to the capillary walls then leads to exudation of protein-rich fluid, erythrocytes, and platelets into the lungs. The cellular and proteinaceous exudate eventually fills and obliterates the distal airspaces, as shown in Figure 24.1. The inflammatory exudate contains fibrin, which can accumulate and produce irreversible pulmonary fibrosis if the inflammation does not resolve within a few weeks.

Predisposing Conditions

ARDS is not a primary disorder, but is a consequence of a variety of infectious and noninfectious conditions. The typical conditions that predispose to ARDS are listed in Table 24.1 (1). The most frequent offenders are pneumonia, extrapulmonary sepsis, septic shock, aspiration of gastric contents, blood transfusions, noncardiogenic shock, and multisystem trauma (1). The shared feature among all these conditions is the activation of neutrophils in the inflammatory response (see Figure 17.1), which is the principal inciting event in ARDS. About 10% of cases of ARDS have no identifiable source (1).

COVID-19 and ARDS

The pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is generally classified as ARDS when it causes hypoxemic respiratory failure, and at the height of the coronavirus (COVID-19) pandemic, ARDS was reported in one of every three patients hospitalized with COVID-19 (6). However, severe hypoxemia from COVID-19 is often associated with little or no change in lung compliance (distensibility) (7), which is not a characteristic finding in severe ARDS. Therefore, COVID-19 is a unique type of ARDS, which is relevant because many of the recent studies of ARDS have been in patients with COVID-19, and the results may not apply to other cases of ARDS.

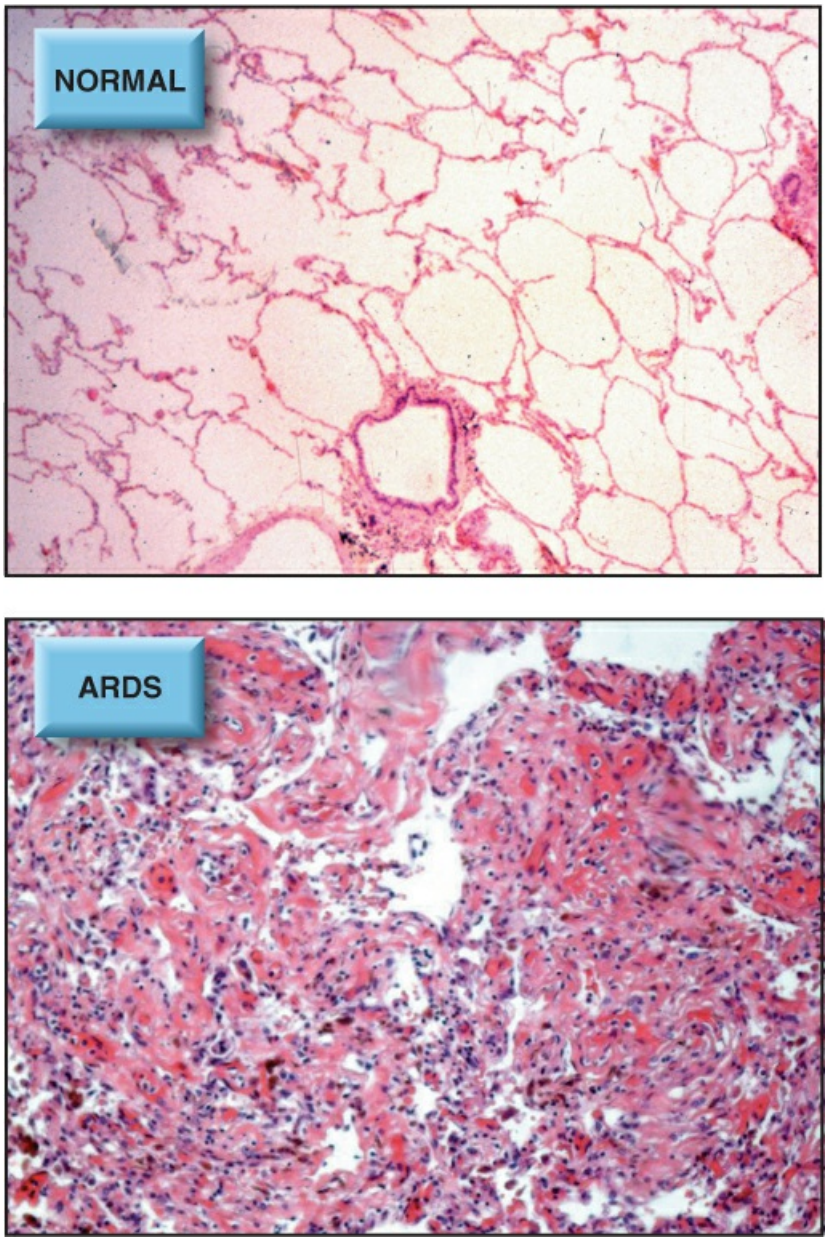


FIGURE 24.1 Microscopic appearance of a normal lung, which shows an abundance of distal airspaces separated by thin segments of tissue that contain the pulmonary capillaries, and a lung in the advanced stages of ARDS, which shows a dense infiltration of leukocytes and proteinaceous material that fills and obliterates the distal airspaces. Photomicrograph of ARDS courtesy of Martha L. Warnock, MD. Image digitally retouched.

TABLE 24.1 Predisposing Conditions for ARDS

Infection-Related	Noninfectious
Pneumonia (60%)	Gastric Aspiration (14%)
Extrapulmonary Sepsis (16%)	Blood Transfusions (4%)
Septic Shock (8%)	Multisystem Trauma (4%)
	Pulmonary Contusion (6%)
	Inhalation Injury (2%)

	Drug Overdose (2%)

From Reference 1. The prevalence of each condition is in parentheses. The total prevalence exceeds 100% because some cases had more than one predisposing condition.

THE DIAGNOSIS OF ARDS

Clinical Features

The clinical criteria for the diagnosis of ARDS are listed in Table 24.2. The principal criteria include the acute onset of hypoxemic respiratory failure (as defined by a PaO_2/FIO_2 ratio ≤300 mm Hg with PEEP = 5 cm H_2O), bilateral infiltrates on the chest x-ray, the presence of a predisposing condition for ARDS, and no evidence of left heart failure or fluid overload (8). The earliest signs of ARDS are progressive dyspnea and hypoxemia. The chest x-ray can be unrevealing in the early hours after symptom onset, but bilateral pulmonary infiltrates begin to appear within 24 hours. The respiratory failure from ARDS often warrants admission to the ICU, and 80% of these patients require intubation and mechanical ventilation, typically in the first 48 hours after presentation (1).

Severity of Illness

ARDS has a severity-of-illness rating based on the PaO_2/FIO_2 ratio: i.e., a ratio of 201–300 mm Hg is mild illness, 100–200 mm Hg is moderate illness, and <100 mm Hg is severe illness (1). The in-hospital mortality rate is about 35% for mild ARDS, 40% for moderate ARDS, and 45% for severe ARDS (1).

TABLE 24.2 Diagnostic Criteria for ARDS

1. Acute onset (within 7 days).
2. Bilateral alveolar infiltrates on chest x-ray.
3. PaO_2/FIO_2 ≤300 mm Hg with PEEP ≥5 mm Hg.
4. No evidence of left heart failure or fluid overload.
5. The presence of a predisposing condition.

From Reference 6. FIO_2 = fractional concentration of inhaled oxygen, PEEP = positive end-expiratory pressure.

Diagnostic Problems

Despite almost 50 years of clinical experience with ARDS, errors in diagnosis (both overdiagnosis and underdiagnosis) are reported in as many as 50% of cases (1,9). The following sections highlight some of the diagnostic pitfalls.

PEEP as a Diagnostic Criterion

The standard definition of ARDS includes a requirement for positive end-expiratory pressure (PEEP), as shown in Table 24.2 (item #3). This has been questioned (2), since the application of PEEP requires intubation and mechanical ventilation, which precludes cases of ARDS that do not require mechanical ventilation.

Chest Radiography

The classic radiographic appearance of ARDS is shown in the top panel of Figure 24.2. The infiltrate has a finely granular or "ground-glass" appearance, and is evenly distributed in all lung fields, with no evidence of a pleural effusion. Unfortunately, the *characteristic features on chest x-ray are present in only 15–25% of cases of ARDS* (10,11). More localized infiltrates are more common (10), as demonstrated by the chest x-ray in the lower panel of Figure 24.2, which shows infiltrates that are confined to the lower lung fields, and a probable left-sided pleural effusion. This chest x-ray is from a case of ARDS secondary to gram-negative septicemia, and could be mistaken for cardiogenic pulmonary edema.

The chest x-ray is a major source of error in the diagnosis of ARDS. When compared with computed tomography (CT) of the chest (the most reliable imaging modality for ARDS), chest x-rays have a negative predictive value of only 47% in ARDS (10), which means a negative chest x-ray has about a 50% chance of excluding the presence of ARDS. This is no better than predicting heads or tails on a coin toss.

Lack of Specificity

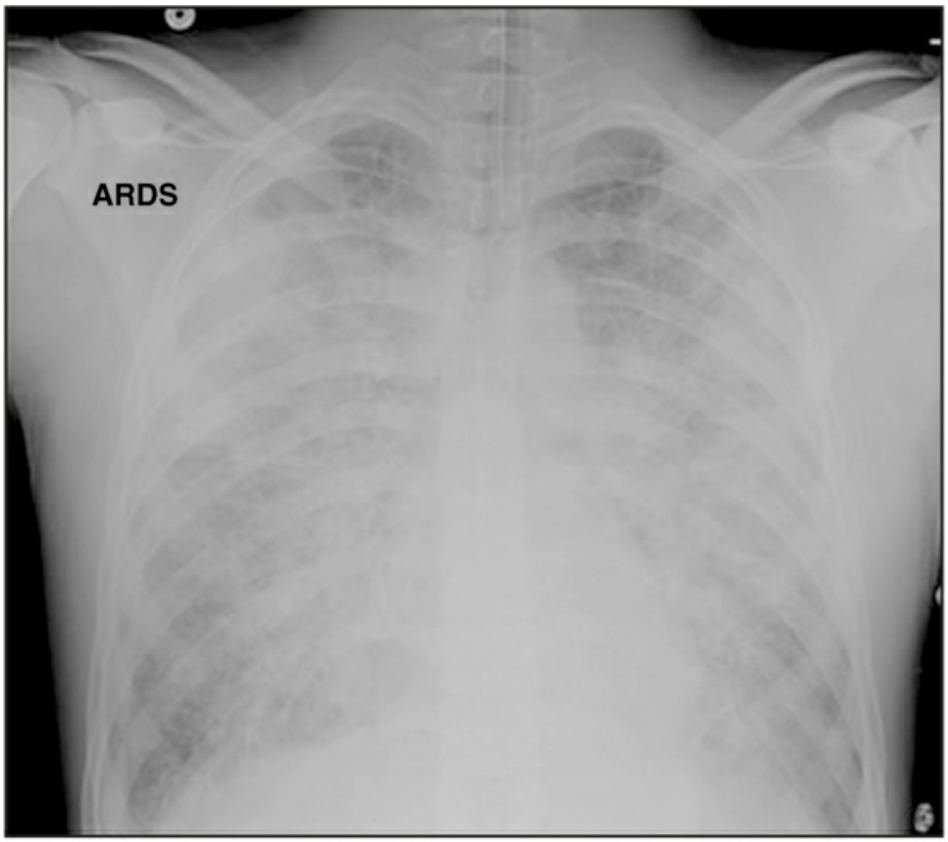
Many of the diagnostic criteria for ARDS are shared with other causes of acute respiratory failure (e.g., pneumonia), and this creates a risk for misdiagnoses. This is demonstrated by an autopsy study showing pathological evidence of ARDS in only 50% of the patients who died with a clinical diagnosis of ARDS (9). The likelihood of identifying ARDS in this study was 50%, similar to the performance of chest x-rays mentioned earlier.

Pitfalls of the Wedge Pressure

When the chest-x-ray shows overlapping features of ARDS and cardiogenic pulmonary edema (like the one in Figure 24.3), the pulmonary artery "wedge" pressure has been used to distinguish between these two conditions: i.e., a wedge pressure ≤18 mm Hg is considered evidence of ARDS (12). This is problematic because *the wedge pressure is NOT a measure of capillary hydrostatic pressure*, as explained in Chapter 8 (see section titled WEDGE PRESSURE). The left atrial (wedge) pressure is lower than the capillary hydrostatic pressure, which creates the pressure gradient needed for flow in the pulmonary veins. This means that *a normal wedge pressure does not exclude the diagnosis of cardiogenic (hydrostatic) pulmonary edema*. The erroneous interpretation of the wedge pressure has undoubtedly led to the overdiagnosis of ARDS.

Computed Tomography

Computed tomographic (CT) imaging has become a standard practice in the diagnosis of ARDS, and CT images can have a different appearance at different stages of the disease. This is demonstrated in Figure 24.3. The CT image in the top panel is from the early stage of ARDS, and shows dense consolidation in the posterior lung regions, which are the dependent lung regions in the supine position. The CT image in the lower panel is from an advanced stage of ARDS (13), and shows diffuse, reticulated infiltrates (that may represent pulmonary fibrosis) in all lung fields. The CT appearance in ARDS has important implications for management (see later).


ARDS

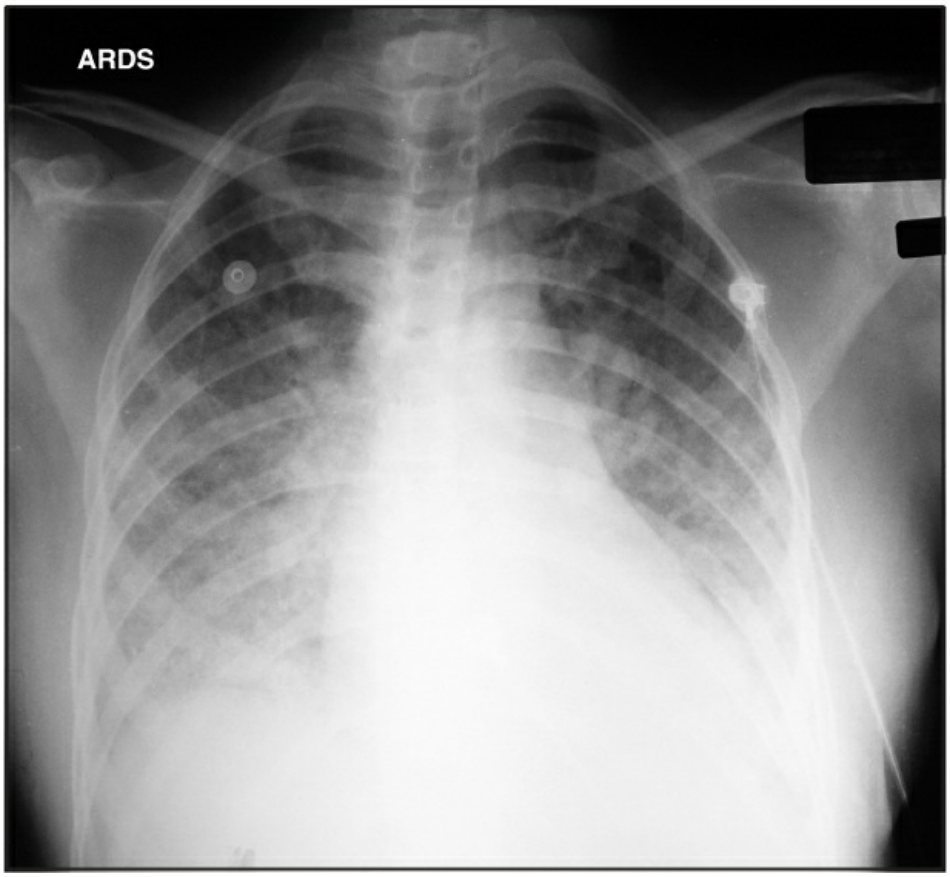

ARDS

FIGURE 24.2 Variable chest x-ray appearance in ARDS. The top panel shows the classic radiographic appearance, with finely granular infiltrates that are evenly distributed throughout both lungs. The bottom panel (which is from a case of ARDS secondary to gram-negative septicemia) shows bilateral infiltrates that are confined to the lower lung fields, with obliteration of the left hemidiaphragm suggesting a pleural effusion.

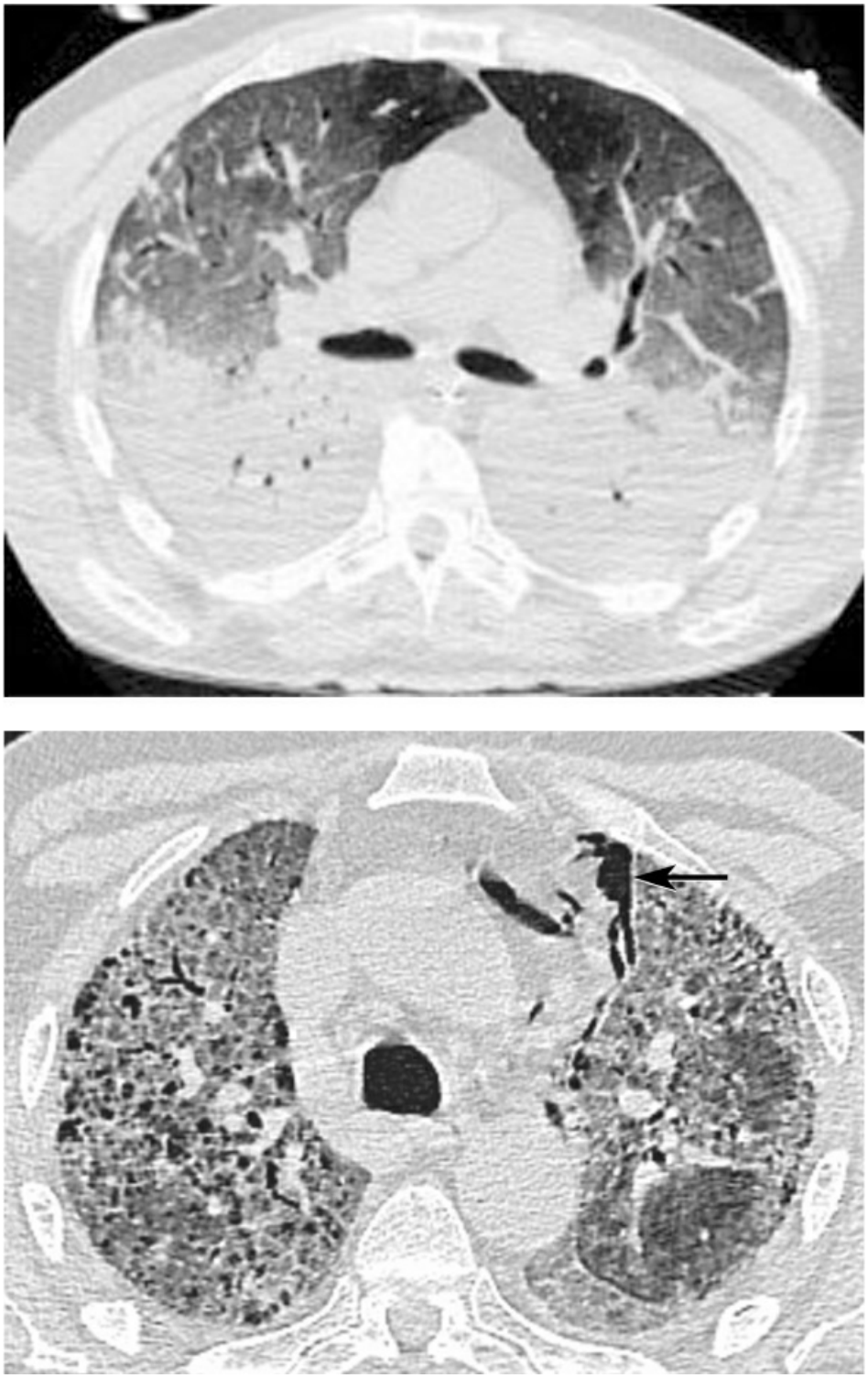


FIGURE 24.3 CT images at different stages of ARDS. The image in the top panel is from the

early stage of ARDS, and shows dense consolidation in the posterior lung regions. The image in the lower panel is from an advanced stage of ARDS, and shows reticulated infiltrates in all lung fields, with a pneumo-mediastinum (indicated by the arrow). Images from Reference 7 (top panel) and Reference 13 (lower panel).

NON-VENTILATOR MANAGEMENT

Other than treatment of the predisposing condition (if available), drug therapies aimed at improving survival in ARDS have been marked by failure rather than success. Failed therapies include surfactant (in adults), inhaled nitric oxide, inhaled prostacyclins, statins, corticosteroids (with a few exceptions described later), neuromuscular blockers, β-receptor agonists, interferon β-1a, and granulocyte-colony stimulating factor (14). As a result, the management of ARDS consists primarily of general supportive measures, including mechanical ventilation. This section focuses on support measures other than mechanical ventilation, especially ones that have a proven impact.

Patient Self-Induced Lung Injury (P-SILI)

Avoiding intubation is a priority in ARDS. However, breathing with increased effort (as often occurs in patients with respiratory failure) can be a source of lung injury; a phenomenon known as “patient self-induced lung injury” (P-SILI) (15). This injury is attributed to large negative swings in intrathoracic pressure created by vigorous breathing efforts, as they can promote “negative pressure pulmonary edema” (16). The presumed mechanism is incomplete transmission of the negative intrathoracic pressures across the walls of intrathoracic blood vessels, which increases the transmural pressure that drives fluid out of the pulmonary capillaries (see Figure 24.4). This tendency for edema formation is enhanced further by the “leaky” pulmonary capillaries in ARDS.

The other consequence of increased breathing efforts is an increase in inhaled (tidal) volumes, which can damage the lungs in ARDS by overstretching alveoli in unaffected areas of lung. This is similar to the “volutrauma” in ventilatory-induced lung injury (see later). Of interest, P-SILI can also occur during mechanical ventilation in patients who “overbreathe” the ventilator.

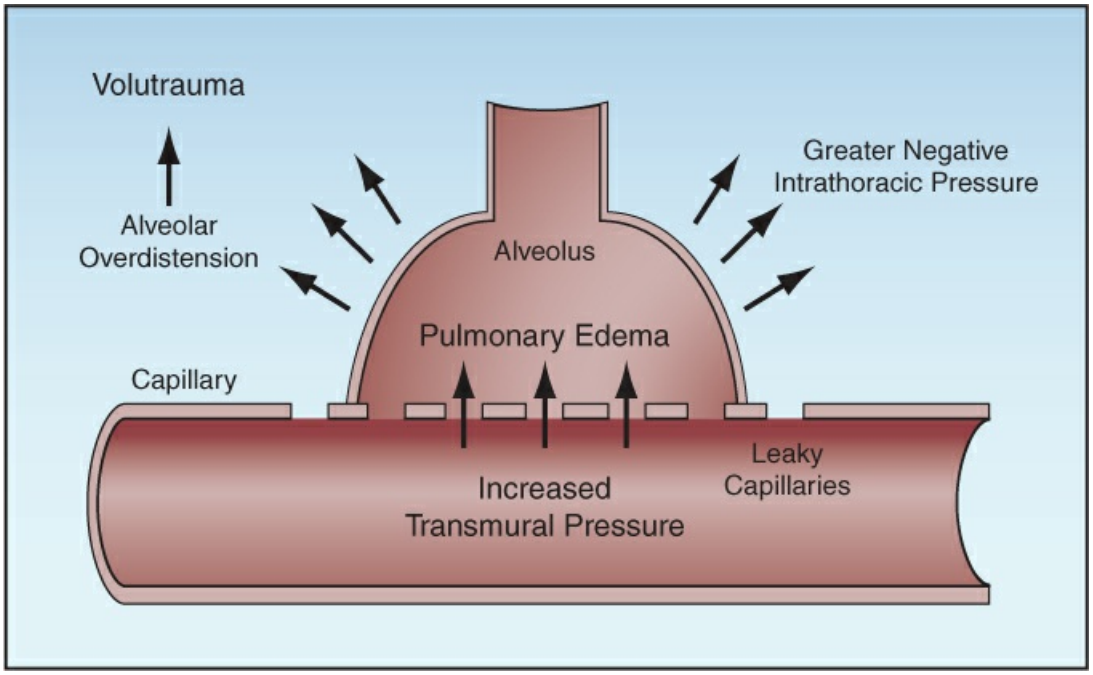


FIGURE 24.4 Schematic illustration of the factors involved in "patient self-induced lung injury" (P-SILI). See text for explanation.

Implications

The risk of P-SILI implies that delays to intubation and mechanical ventilation can have deleterious consequences for patients who continue to have labored breathing. This highlights the importance of measures (e.g., oxygen therapy, sedation) that can relieve the sense of dyspnea and promote comfortable breathing. For patients who continue to breathe with increased efforts, intubation and mechanical ventilation is advised sooner rather than later.

Oxygen Therapy

Providing supplemental O_2 is the first concern in patients with hypoxemic respiratory failure. If conventional O_2 therapy (which delivers O_2 at rates up to 15 L/min) does not correct the hypoxemia, then a trial of high-flow nasal O_2 is warranted.

High-Flow Nasal O_2

High-flow nasal oxygen (HFNO) provides heated and humidified O_2 at rates up to 40–60 L/min through specially-designed nasal prongs, and the circuit has an oxygen regulator that allows independent adjustments of the FIO_2 (see Figure 25.5). Studies of ARDS from COVID-19 (17) have shown that patients treated with HFNO had fewer intubations than patients treated with conventional O_2 therapy (although there was no difference in mortality rate). The reduction in intubation rate with HFNO is not a consistent finding (18), but it is now recommended as a *replacement* for conventional O_2 therapy in patients with hypoxemic respiratory failure (2). The advantage of HFNO over conventional O_2 therapy is the ability to produce comfortable breathing (which is attributed to the high flow rate). This not only promotes patient well-being, it also reduces the risk of patient-induced self injury (P-SILI), and thus could limit the extent of lung

injury.

Don't Forget O_2 Toxicity

The use of high-flow O_2 to delay or prevent intubation and mechanical ventilation often exposes patients to high concentrations of O_2 (i.e., F_IO_2 ≥70%) for prolonged periods of time, and this introduces the risk of pulmonary O_2 toxicity. Attention to the risk of pulmonary O_2 toxicity is emphasized by the following statements:

. Critically ill patients are often deficient in protective antioxidants (e.g., glutathione) (19), and thus are susceptible to O_2 toxicity.

. High levels of O_2 accelerate the damaging effects of mechanical ventilation (20).

. The lung injury in pulmonary O_2 toxicity is identical to ARDS, so cases of ARDS that progress while breathing high concentrations of O_2 could be the result of O_2 toxicity.

The above concerns highlight the importance of limiting the concentration of inhaled O_2 whenever possible. (The toxic effects of O_2 are presented in Chapter 25.)

Noninvasive Ventilation

Noninvasive ventilation (NIV), which is described in Chapter 26 is a popular intervention in the early management of ARDS, and is most successful in preventing intubation in patients with mild ARDS (i.e., PaO_2/F_IO_2 = 201–300 mm Hg) (21). This is shown in Figure 24.5 (panel on the left). The panel on the right shows that patients who fail NIV and require intubation have a much higher mortality rate. Although this is likely a reflection of the underlying severity of illness, it is also possible that patient self-induced lung injury (P-SILI) plays a role in the adverse outcomes.

P-SILI and NIV Failure

Failure to increase the PaO_2/F_IO_2 ratio after one hour of NIV indicates a poor response, and intubation should be considered at this time. Patients who fail NIV typically have increased tidal volumes (i.e., ≥9.5 mL/kg predicted body weight) (22), indicating an increased breathing effort, and suggesting the possible role of P-SILI in NIV failure. As such, intubation should be a serious consideration when the PaO_2/F_IO_2 ratio does not improve and the patient continues to have increased breathing efforts.

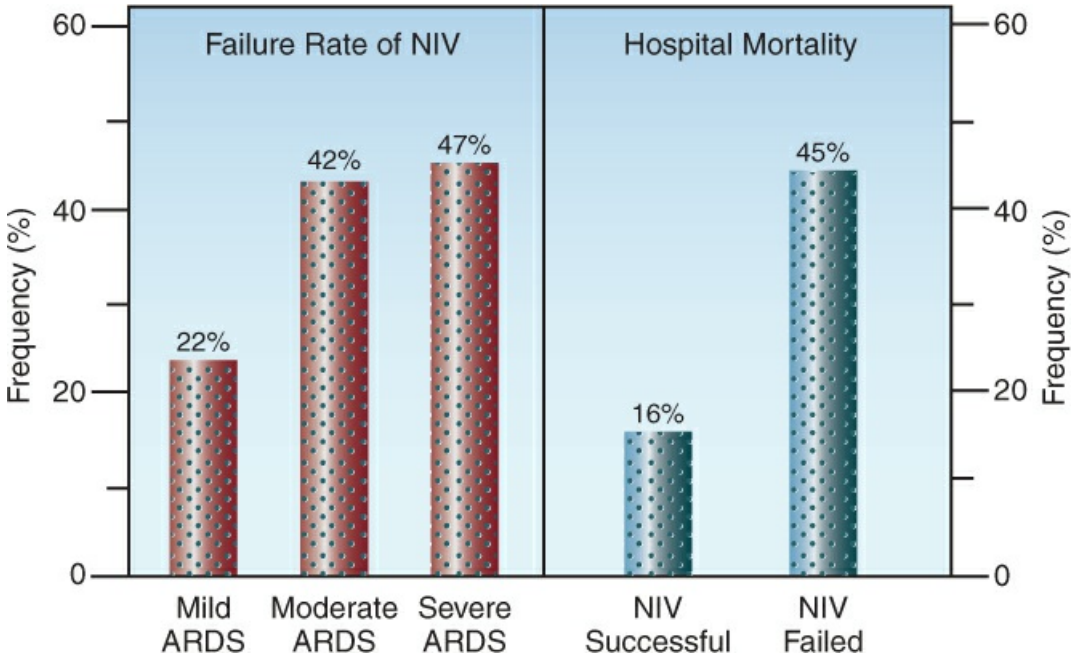


FIGURE 24.5 Observations on the use of noninvasive ventilation (NIV) for the first 48 hours after the diagnosis of ARDS. Panel on the left shows that NIV was most successful in preventing intubation in patients with mild ARDS (PaO_2/FIO_2 = 201–300 mm Hg) and the panel on the right shows that failure of NIV has a higher mortality rate. Data from Reference 21. See text for further explanation.

Fluid Management

The lungs are susceptible to fluid accumulation in ARDS because of the leaky pulmonary capillaries, so fluid management should be aimed at avoiding or correcting a positive fluid balance, which can reduce the duration of mechanical ventilation (23). This goal is best served by attention to daily fluid balances, with the use of diuretics to correct fluid excess. The positive intrathoracic pressures during mechanical ventilation will magnify the drop in cardiac output in response to hypovolemia, so it is also important to avoid fluid deficits, which can promote systemic hypoperfusion and aggravate the multiorgan dysfunction that often accompanies ARDS (24).

Corticosteroid Therapy

You may already be aware that steroids enjoy a popularity in clinical medicine that is far greater than deserved, and ARDS provides an example of this phenomenon. There have been innumerable trials of steroid therapy in ARDS since the disease was first described almost 50 years ago, yet the role of steroid therapy in ARDS continues to be debated (13,25), and the recommendations seem to change every 5–10 years. (Simply stated, if a drug effect is not convincing after 50 years, it's time to move on.)

Clinical trials of steroid therapy in ARDS have produced inconsistent results (13,25,26), which is partly attributed to the heterogeneity of the ARDS cases, and to differences in the steroid regimens. The following recommendations are based on evidence of improved outcomes with steroid therapy in at least some clinical trials. This information is summarized in Table 24.3.

COVID-19

Dexamethasone (6 mg IV or PO daily for up to 10 days) is recommended for cases of COVID-19 that require supplemental O_2 or some form of ventilatory assistance (noninvasive or invasive mechanical ventilation) (27). There is no evidence that this steroid regimen impairs clearance of the SARS-CoV-2 virus (28).

Moderate-to-Severe ARDS

The most recent clinical practice guideline includes a weak recommendation for steroid therapy the first 14 days for patients with moderate-to-severe ARDS (PaO_2/FIO_2 ratio <200 mm Hg with PEEP = 10 cm H_2O) (29). There are two steroid regimens (see Table 24.3). Both use intravenous infusions of methylprednisolone. One regimen is initiated in the early stage of disease (i.e., first 72 hours), and uses a methylprednisolone dose of 1 mg/kg/day (ideal body weight). The other regimen is used for ARDS that persists for 7–14 days, and uses a methylprednisolone dose of 2 mg/kg/day. (The latter regimen is aimed at the fibrinoproliferative phase of ARDS, which begins 7–14 days after the onset of illness, and culminates in irreversible pulmonary fibrosis) (30). Both steroid regimens are continued for 14 days, with a slow taper over this time.

Adverse Effects

Hyperglycemia is the most frequently reported side effect of steroid therapy for ARDS (25). The most feared complication is an acute myopathy that is typically associated with the combined use of high dose steroids and neuromuscular blocking agents, but this is rare (31).

TABLE 24.3 Recommendations for Corticosteroid Therapy in ARDS

Condition	Drug Regimen
COVID-19 that requires any of the following: a. Oxygen therapy b. Noninvasive ventilation c. Mechanical ventilation	Dexamethasone: 6 mg (IV or PO) once daily for up to 10 days.
Moderate-to-Severe ARDS in the first 72 hrs after onset.	Methylprednisolone: 1 mg/kg/day (IBW) by continuous infusion, and taper slowly over 14 days. Can eventually switch to PO therapy using once daily dosing.
Moderate-to-Severe ARDS that persists 7–14 days after onset	Same regimen as above, except the methylprednisolone dose is 2 mg/kg/day (IBW).

From References 27,29. IBW = ideal body weight.

Prone Positioning

CT images like the one at the top of Figure 24.3, which shows a dense consolidation in the posterior lung regions (7,32), prompted studies of prone positioning to redirect blood flow to better aerated anterior lung regions.

Physiological Effects

Prone positioning not only increases blood flow in the anterior region of the lungs, it also promotes aeration in posterior lung segments (33). Both effects serve to improve arterial oxygenation and facilitate CO_2 removal. During spontaneous breathing, a switch to the prone position reduces both the respiratory rate and the work of breathing (34), possibly by increasing lung compliance (i.e., distensibility). There is also a decrease in pulmonary artery pressures (35), which helps alleviate right heart strain.

When to Use

Prone positioning was originally used as a rescue maneuver for refractory hypoxemia in mechanically ventilated cases of ARDS, but the COVID-19 pandemic shifted attention to the use of prone positioning in spontaneously breathing patients, where it proved effective in preventing intubation in select groups of patients. The current indications for prone positioning in ARDS are shown in Table 24.4, and are based on the observations summarized below.

. In spontaneously breathing patients with ARDS, prone positioning can reduce the need for intubation and mechanical ventilation, but only in patients who are receiving high-flow nasal O_2 or noninvasive ventilation (36). Despite fewer intubations in these patients, there is no impact on the mortality rate (36).

. In mechanically ventilated patients with ARDS, prone positioning has a proven survival benefit in patients with moderate-to-severe disease (i.e., PaO_2/FIO_2 <150 mm Hg with PEEP ≥5 cm H_2O, or an FIO_2 ≥60% with PEEP of 10 cm H_2O) who are ventilated at low tidal volumes (about 6 mL/kg predicted body weight) (37).

CONCERNS: The ability of prone positioning to prevent intubation is derived from studies of COVID-19 ARDS, and the results may not apply to ARDS from other sources (because COVID-19 is a unique form of ARDS, as mentioned earlier). In addition, the survival benefit of prone positioning in mechanically ventilated patients is not a consistent finding (38).

One proposal that deserves attention is *the possibility that the success of prone positioning is dependent on appearance of the CT scan* (7), with a greater likelihood of success when the CT scan shows dense consolidation in the posterior lung regions.

TABLE 24.4 Prone Positioning in ARDS

Indications	Contraindications†
1. To prevent intubation in patients who are breathing spontaneously but require high-flow nasal O_2 or noninvasive ventilation. 2. To promote survival in mechanically ventilated patients with moderate-to-severe ARDS* who are ventilated with a tidal volume of ~6 mL/kg (predicted body weight).	Active hemorrhage Spinal instability Multiple fractures Increased ICP Recent tracheostomy or sternotomy (2 wks)

* PaO_2/FIO_2 <150 mm Hg and FIO_2 ≥60%, with PEEP ≥5 cm H_2O.

†Includes only absolute contraindications, from Reference 40. ICP = intracranial pressure.

CONTRAINDICATIONS: The absolute contraindications for prone positioning are listed in Table 24.4 (39). Relative contraindications include circulatory shock, pregnancy, recent life-threatening arrhythmias, and functioning chest tubes (39). The use of vasopressors is not a contraindication if the clinical condition is stable or improving.

How to Use

ICUs usually have a protocol for prone positioning, and the following are some important considerations for this protocol.

DURATION: The duration of prone positioning is an important determinant of success. For spontaneously breathing patients, at least 8 hours of prone positioning daily (in a single session) is recommended (40). For mechanically ventilated patients, at least 16 hours in the prone position each day is advised (2).

EVALUATION: A beneficial response (e.g., increase in the PaO_2/FIO_2 ratio, increase in lung compliance) should be seen after the first session of prone positioning; if the improvement persists for 4 hours after the session, then prone positioning is no longer needed (38). If there no evidence of benefit after a session of prone positioning, then further sessions are not warranted.

COMPLICATIONS: Complications of prone positioning include patient discomfort, vomiting, brachial plexus injury, pressure sores, dislodgement of endotracheal tubes and vascular catheters, and transient arrhythmias. These are generally infrequent (39).

MECHANICAL VENTILATION IN ARDS

ARDS is the most common cause of acute hypoxemic respiratory failure that requires mechanical ventilation (1), so the discovery that *mechanical ventilation can be a source of lung injury that resembles ARDS* has profound implications. This section describes the lung injury related to mechanical ventilation, and the strategy that is designed to limit this injury.

Ventilator-Induced Lung Injury

Positive pressure mechanical ventilation rose to prominence during the polio epidemic in the 1950s, and it did not take long to recognize that positive pressure lung inflations could rupture distal airspaces and produce pneumothoraces. A more complete picture of the lung injury from mechanical ventilation emerged in 1967 as the *respirator lung syndrome* (41), which was described as diffuse inflammatory infiltration in the lungs with hyaline membrane formation. Later studies showed that mechanical ventilation produces stress fractures in the alveolar capillary interface, as shown in Figure 24.6, and this damage promotes inflammation and fluid accumulation in the lungs (42). This condition is now known as “ventilator-induced lung injury” (VILI) (42). Multiple factors are involved in this injury, as described next.

Volutrauma

When the lungs are stiff (as occurs in ARDS), ventilators must generate higher pressures to deliver a given tidal volume, and VILI was initialy considered to be a pressure-related injury

(i.e., barotrauma). However, a landmark study in the 1980s showed that VILI is the result of high inflation *volumes*, not high inflation airway pressures (43). Instead of barotrauma, the culprit in VILI is *volutrauma*.

There are two predisposing factors for volutrauma. The first is the high tidal volumes used during mechanical ventilation. When positive pressure ventilation was first introduced, large tidal volumes were adopted to reduce the tendency for atelectasis during controlled ventilation (44). The traditional tidal volumes during mechanical ventilation are 12−15 mL/kg (ideal body weight), which is about twice the normal tidal volume (6−7 mL/kg). The second predisposing factor is the reduced volume capacity of the lungs in ARDS, as demonstrated in the CT scan at the top of Figure 24.3. Thus, tidal volumes that are twice normal are being forced into lungs that are operating at 50% capacity. This volume mismatch is the principal source of alveolar rupture, and disruption of the alveolar-capillary interface.

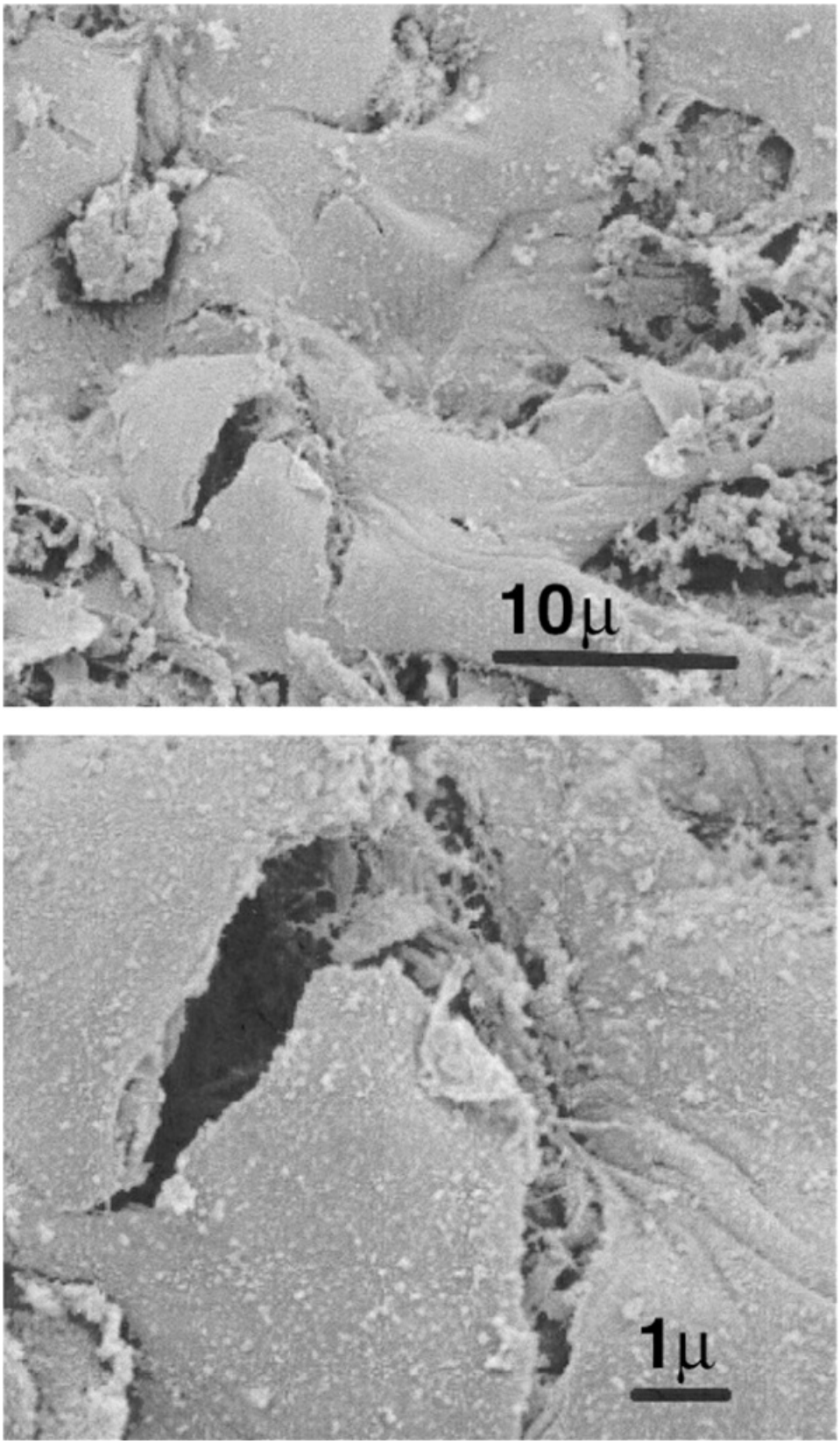


FIGURE 24.6 Electron micrographs of a (postmortem) lung specimen from a patient with ARDS, which shows a tear in the alveolar-capillary interface from alveolar overdistension during

mechanical ventilation (i.e., volutrauma). Images from Reference 41, digitally retouched.

Atelectrauma

The decrease in lung distensibility in ARDS results in the collapse of small airways at the end of expiration, followed by reopening of the airways when the tidal volume is delivered. This cyclical opening and closing of the small airways creates shear forces that damage the airway epithelium (45). This phenomenon has been given the name *atelectrauma* (46), and it can be minimized or eliminated by applying positive end-expiratory pressure (PEEP) to hold the small airways open at the end of expiration.

Biotrauma

The physical forces involved in high-volume mechanical ventilation in ARDS can trigger the release of proinflammatory cytokines in the lungs, and these can reach the systemic circulation and produce a systemic inflammatory response (47). This occurs in the absence of structural damage in the lungs, and is known as *biotrauma*. The systemic inflammatory response from biotrauma can promote inflammatory injury in other organs, which means that *mechanical ventilation can be a source of extrapulmonary organ injury and multiorgan failure* (48)!

Lung Protective Ventilation

Lung protective ventilation employs reduced tidal volumes to protect against volutrauma and biotrauma, and uses positive end-expiratory pressure (PEEP) to prevent atelectrauma. A protocol for lung protective ventilation is shown in Table 24.5. The goal is a tidal volume of 6 mL/kg, using *predicted body weight*, which is the body weight associated with normal lung volumes. Note that another goal is an end-inspiratory "plateau" pressure ≤30 cm H_2O. This pressure is described in Chapter 27, and is a reflection of the peak pressure in the alveoli. A peak alveolar pressure of >30 cm H_2O creates a risk of alveolar rupture, hence the goal of lung protective ventilation is a peak alveolar pressure ≤30 cm H_2O.

TABLE 24.5 Protocol for Lung Protective Ventilation in ARDS

First Stage	1. Calculate patient's predicted body weight (PBW)†. Males: PBW = 50 + [2.3 x (height in inches – 60)] Females: PBW = 45.5 + [2.3 x (height in inches – 60)] 2. Set initial tidal volume (V_T) at 8 mL/kg PBW. 3. Add positive end-expiratory pressure (PEEP) of 5 cm H_2O. 4. Select the lowest FIO_2 that achieves an SpO_2 of 88–95%. 5. Reduce V_T by 1 mL/kg every 2 hrs until V_T = 6 mL/kg.
Second Stage	1. When V_T = 6 mL/kg, measure plateau pressure (Ppl). 2. If Ppl >30 cm H_2O decrease V_T in 1 mL/kg increments until Ppl <30 cm H_2O or V_T. = 4 mL/kg.
Third Stage	1. Monitor blood gases for respiratory acidosis. 2. If pH = 7.15–7.30, increase respiratory rate (RR) until pH >7.30 or RR = 35 bpm. 3. If pH <7.15, increase RR to 35 bpm. If pH is still <7.15, increase V_T in 1 mL/kg increments until pH >7.15.

Optimal Goals	V_T = 6 mL/kg, Ppl ≤30 cm H_2O, SpO_2 = 88–95%, pH = 7.30–7.45.

Adapted from the protocol developed by the ARDS Network, available at www.ardsnet.org.

†Predicted body weight is the weight associated with normal lung volumes.

Positive End-Expiratory Pressure

Lung protective ventilation employs a positive end-expiratory pressure (PEEP) of 5 cm H_2O, to prevent the collapse of small airways at the end of expiration. This is aimed at preventing the cyclical opening and closing of small airways that produces atelectrauma. (PEEP is described further in Chapter 27).

Permissive Hypercapnia

Low volume ventilation impairs CO_2 removal, and promotes hypercapnia. This is allowed as long as there is no evidence of harm (e.g., CO_2 narcosis). The limits of tolerance to hypercapnia and respiratory acidosis are unclear, but data from clinical trials of "permissive hypercapnia" show that arterial PCO_2 levels of 60–70 mm Hg and arterial pH levels of 7.2–7.25 are safe for most patients (49). The target pH is 7.30–7.45 in the protocol for lung protective ventilation.

Survival Benefit

Lung protective ventilation is the only ventilatory strategy that has shown a survival benefit in ARDS (49,50); as a result, it is strongly recommended as the preferred method of mechanical ventilation in ARDS (2,3). However, the benefit of lung protective ventilation is not a consistent finding (51), and it has not gained widespread acceptance. In one survey, fewer than two-thirds of patients with ARDS received tidal volumes ≤8 mL/kg predicted body weight (1).

Airway Pressure Release Ventilation

A different approach to mechanical ventilation in ARDS is to open collapsed alveoli with a mode of ventilation known as "airway pressure release ventilation (APRV), which uses prolonged periods of spontaneous breathing at high intrathoracic pressures, interspersed with brief periods of pressure release. This is shown in Figure 24.7. The prolonged periods of breathing at high pressures are designed to open collapsed alveoli, which will increase arterial oxygenation and reduce lung stiffness, while the pressure release facilitates CO_2 elimination (52). The high pressure is usually set at the last plateau pressure (not to exceed 30 cm H_2O to prevent alveolar overdistension), while the low pressure is set at 5 cm H_2O.

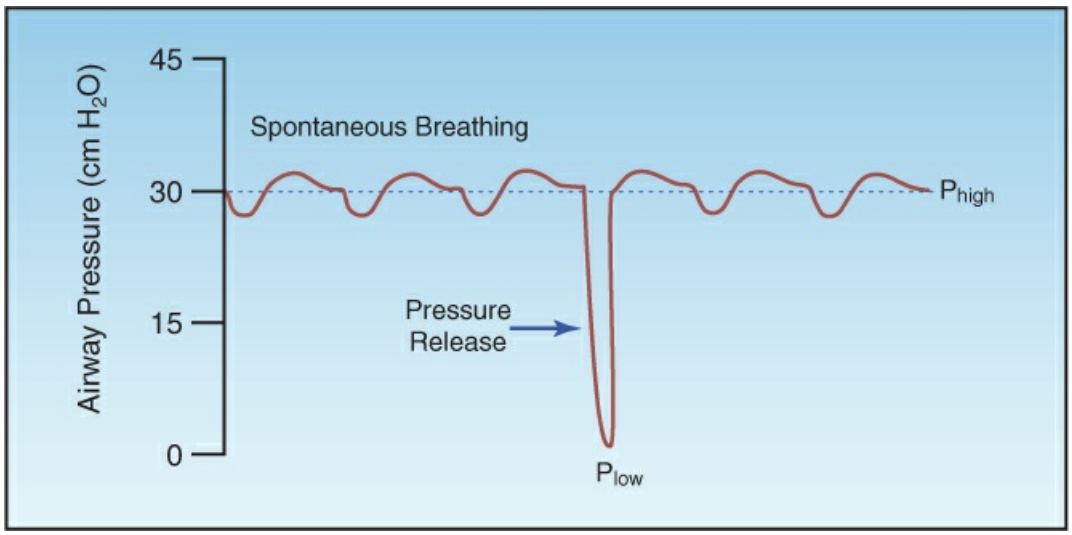


FIGURE 24.7 The pattern of ventilation in "airway pressure release ventilation" (APRV). See text for explanation.

One study comparing APRV with lung protective ventilation showed that APRV reduced the time on mechanical ventilation, but without a survival benefit (53). There are also anecdotal claims of success with APRV (the author included), but more studies are awaited.

Therapeutic Misdirection?

Mechanical ventilation is not a treatment for ARDS—in fact, the benefit of lung protective ventilation is to *do less damage* with mechanical ventilation. Moreover, the focus on the lungs in treating ARDS neglects evidence showing that *the principal cause of death in ARDS is multiorgan failure, not respiratory failure* (with the possible exception of COVID-19) (54,55). As many as 70% of deaths in ARDS are the result of multiorgan failure (54), and the mortality rate is directly related to the number of failed organs. This is demonstrated in Figure 24.8, which indicates that the mortality in ARDS is a function of a progressive systemic condition, and it implies that the therapeutic focus on the lungs in ARDS is a prescription for failure.

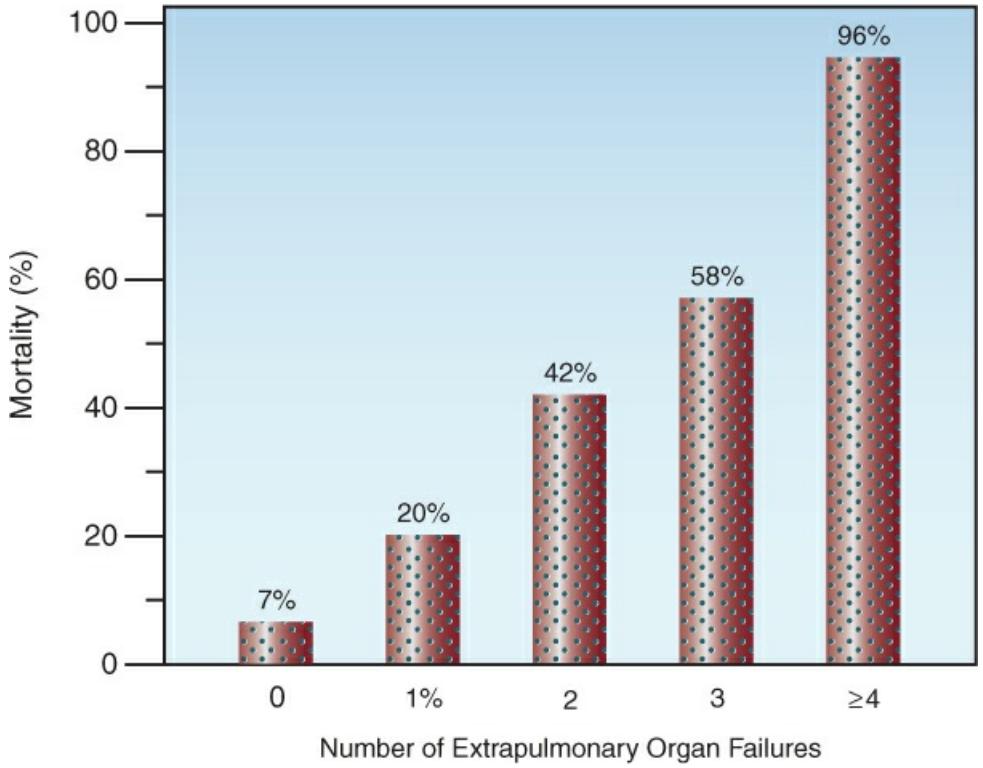


FIGURE 24.8 The relationship between extrapulmonary organ failure and mortality in ARDS. Data from Reference 54 (supplementary material).

Extracorporeal Life Support

Extracorporeal membrane oxygenation (ECMO) is a consideration for the 10–15% of ARDS patients with hypoxemia that is refractory to mechanical ventilation and prone positioning (56). The most recent indications include a PaO_2/FIO_2 ratio <80 mm Hg for at least 6 hours, or <50 mm Hg for at least 3 hours (57). The extracorporeal support strategy for ARDS includes venovenous ECMO with lung protective mechanical ventilation, and extracorporeal CO_2 removal, if needed. The technical aspects of extracorporeal support are beyond the scope of this text, but are available in the bibliography (55,58).

ECMO was first used for a patient with ARDS in 1971, and since that time, numerous studies have shown negative or inconsistent results, with some success in patients with viral pneumonias (e.g., influenza A(H1N1), and COVID-19) (57). Since ECMO is a temporary measure, its success is determined by the reversibility of the ARDS, which can be difficult to predict in the first few weeks of the illness.

A FINAL WORD

The Evils of Inflammation

One of the recurring themes in this book is the dominance of inflammation as a source of organ injury and lethal outcomes in critically ill patients. The destructive actions of inflammation take center stage in ARDS, and also in inflammatory shock (see Chapter 17), and it is possible that

inflammation (not hypoxia) is the principal cause of death in ICUs. (See A FINAL WORD in Chapter 17.)

As is the case with inflammatory shock, there is no specific therapy for ARDS, and management is supportive in nature. Until a remedy is available for the damaging effects of inflammation, conditions like inflammatory shock and ARDS will continue to be a major source of morbidity and mortality.

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Mechanical Ventilation in ARDS

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Section IX

RESPIRATORY MANAGEMENT

All who drink of this remedy will recover . . . except those in whom it does not help, who will die. Therefore, it is obvious that it fails only in incurable diseases.

Claudius Galenus
(Galen)

Chapter 25

Oxygen Inhalation

I brought fire into your midst, and it consumed you, and reduced you to ashes.

Ezekiel (28:17)

There is a fondness for oxygen that is unmatched by any other treatment modality, as is clearly evident in the unbridled use of oxygen in hospitalized patients. The popularity of oxygen is apparent in emergency rooms, where inhaled oxygen is a knee-jerk response to acute illness, and in ICUs, where a patient who is NOT connected to a source of oxygen is a rare sight. Oxygen is given without evidence of tissue need, and without regard for the damaging effects of oxygen. This latter disregard is perplexing, since we protect our food from oxygen (with vacuum sealing, tightly-sealed plastic containers, and cellophane wrapping), yet we don't have the same consideration for our patients.

This chapter begins with an examination of the indications and effects of oxygen inhalation, and then describes the different delivery systems for oxygen. The final section is devoted to the dark side of oxygen: i.e., oxygen-related tissue injury.

INDICATIONS

The first clinical practice guideline for O_2 therapy was published in 1984 (1), and the indication for O_2 therapy was stated as follows:

> Supplemental oxygen therapy is appropriate in acute conditions when there is laboratory documentation of an arterial PO_2 (PaO_2) <60 mm Hg or an arterial O_2 saturation (SaO_2) <90%; *tissue hypoxia is commonly assumed to be present at these laboratory values* [italics mine].

This statement is consistent with the consensus definition of hypoxemia as a PaO_2 <60 mm Hg or an SaO_2 <90%. The most recent guidelines for O_2 therapy (2) include a target SpO_2 (i.e., O_2 saturation by pulse oximetry) of 88−92% for patients with CO_2 retention, and 90−94% for other patients. The major issue with this recommendation is the assumption that tissue oxygenation is impaired when the PaO_2 falls below 60 mm Hg, or the SpO_2 falls below 90%. The following sections shed some light on this issue

Arterial O_2 Content

The threshold for O_2 inhalation is associated with a very small change in the arterial O_2 content. This is demonstrated in Figure 25.1, which shows the arterial O_2 content (CaO_2) at the threshold for both O_2 inhalation and red blood cell (RBC) transfusions (i.e., two interventions aimed at augmenting tissue oxygenation). The CaO_2 was calculated using the equation shown below [see also Equation (9.9)]:

$$CaO_2\ (mL/L) = 1.34 \times Hb \times SaO_2\ (\times 10) \tag{25.1}$$

where 1.34 is the O_2 carrying capacity of hemoglobin (in mL/g), Hb is the hemoglobin concentration (in g/dL), SaO_2 is arterial oxyhemoglobin saturation (expressed as a decimal rather than a percentage), and the factor of 10 is used to convert mL/dL to mL/L. Using normal values for Hb (15 g/dL) and SaO_2 (0.98) yields a CaO_2 of 197 mL/L, which is indicated on the left in Figure 25.1. When the SaO_2 is reduced to 0.90 (the threshold for O_2 therapy), the CaO_2 is 181 mL/L, which is an 8% decrease in CaO_2. In comparison, using a Hb of 7 g/dL as the threshold for RBC transfusions (see Chapter 12), the corresponding CaO_2 is 92 mL/L. which is a 64% decrease from baseline.

The following statements can be derived from the comparisons in Figure 25.1:

. The threshold for O_2 inhalation corresponds to a minor (8%) change in arterial oxygenation.

. Tissue oxygenation is not impaired until the CaO_2 falls below 92 mL/L (the threshold for RBC transfusions), so it cannot be impaired at the much higher threshold for O_2 inhalation.

. It follows then, that the threshold for O_2 inhalation can be lowered.

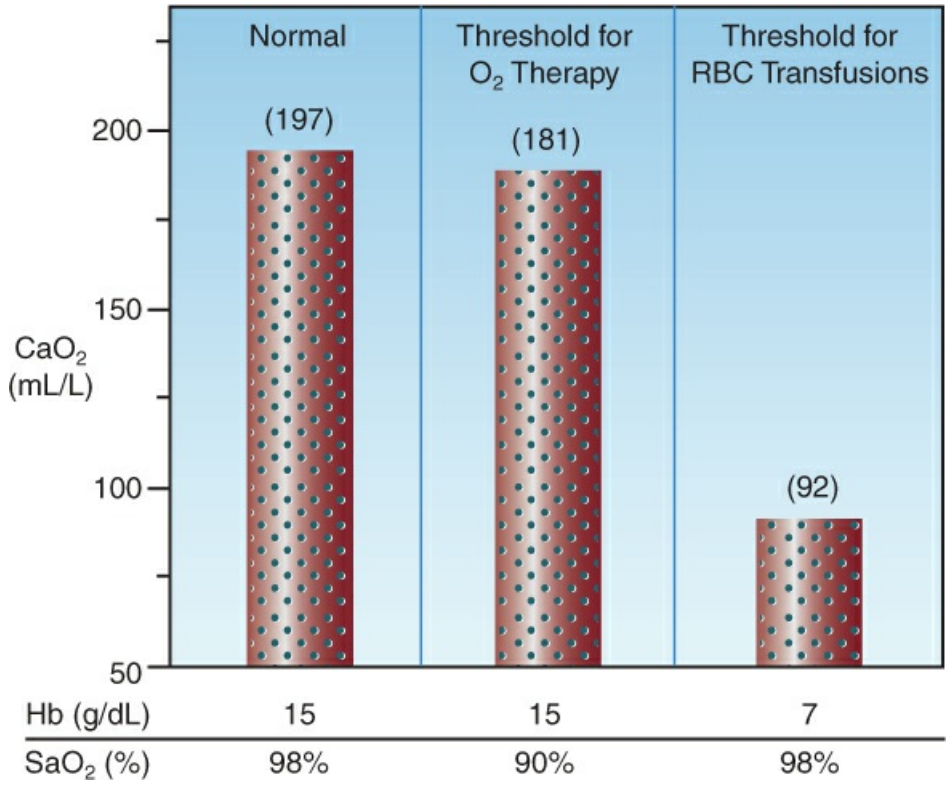

FIGURE 25.1 The arterial O_2 content (CaO_2) at the thresholds for O_2 inhalation (SaO_2 = 90%) and red blood cell transfusions (Hb = 7 g/dL).

Tolerance to Severe Hypoxemia

Since hypoxemia is corrected immediately with supplemental O_2, there is limited information on tolerance to severe hypoxemia. The available information comes from small observational studies and case reports. The data in Table 25.1 is from a study of eight patients with acute exacerbation of COPD who had a PaO_2 below 40 mm Hg while breathing room air for at least one hour (3). The PaO_2, SaO_2, and plasma lactate level is listed for each patient (in ascending order according to severity of hypoxemia), and there is no evidence of impaired tissue oxygenation in any patient, as determined by the normal lactate levels (≤2 mmol/L). Similar observations have been reported in patients with acute respiratory distress syndrome (4), indicating that tolerance to severe hypoxemia is not an adaptation that develops over time.

TABLE 25.1 Tolerance to Severe Hypoxemia

Patient	PaO_2 (mm Hg)	SaO_2 (%)	Lactate (mm/L)
1	22	35	0.9
2	30	54	0.3
3	32	59	0.9
4	33	55	1.6
5	34	65	1.6

6	35	67	2.0
7	37	75	2.0
8	39	76	1.1

From Reference 3.

Hypobaric Hypoxemia

Tolerance to severe hypoxemia was also demonstrated in a study of healthy individuals who were placed in a decompression chamber to simulate the atmospheric pressure at the Summit of Mount Everest (which is 253 mm Hg, or about one-third the pressure at sea level) (5). At this pressure, the PaO_2 was 30 mm Hg and the SaO_2 was 58% (mean values), but the plasma lactate level remained in the normal range at 1.7 mmol/L. Similar findings have been reported in climbers near the summit of Mount Everest without supplemental oxygen (6).

Reinhold Messner

One of the most notable challenges to the dogma about severe hypoxemia came from Reinhold Messner, the most celebrated mountaineer in the history of the discipline, who was the first to climb Mount Everest (elevation 29,029 feet) without the use of supplemental oxygen (a feat he achieved in 1978, along with fellow climber Peter Habeler). Prior to the historic climb, Messner was warned by experts that attempting to summit Mount Everest without supplemental O_2 would be suicidal, as he would lose consciousness and suffer permanent brain damage above an altitude of 26,000 feet (the region known as the "death zone"). However, Messner knew this was an untested claim (like many about oxygen), so he devised a simple test: i.e., using a plane with a depressurized cabin, he was flown to the summit of Mount Everest while breathing ambient air. To the disbelief of the experts, Messner experienced no ill effects as the plane climbed above 26,000 feet (the death zone) and reached its destination. He later wrote, "I had seen the flight through without an oxygen mask, and I was still able to talk, to think, to sense everything" (7).

Implications

In summary, there is considerable evidence indicating that *O_2 inhalation is not based on tissue O_2 needs*; a notion that is supported by the physiological effects of O_2 described in the next section. As a result, the use of O_2 inhalation based on current recommendations results in excessive oxygenation, and this can be detrimental by promoting oxidative tissue injury, as described in the latter part of the chapter.

PHYSIOLOGICAL EFFECTS

Metabolic Rate

The goal of O_2 inhalation is to promote aerobic metabolism. However, there is no evidence that aerobic metabolism is impaired at the threshold for O_2 inhalation, so it seems unlikely that O_2 inhalation will have any impact on aerobic metabolism. This is demonstrated in Figure 25.2,

which shows the effects of breathing 24% and 28% oxygen on the arterial PO_2 (PaO_2) and the rate of aerobic metabolism (VO_2) in patients with acute exacerbation of chronic obstructive lung disease (8). There is a significant increase in the PaO_2 with each increment in inhaled O_2, but the rate of aerobic metabolism remains unchanged. Similar results have been reported in other clinical studies (9,10), indicating that *oxygen inhalation does not promote aerobic metabolism.*

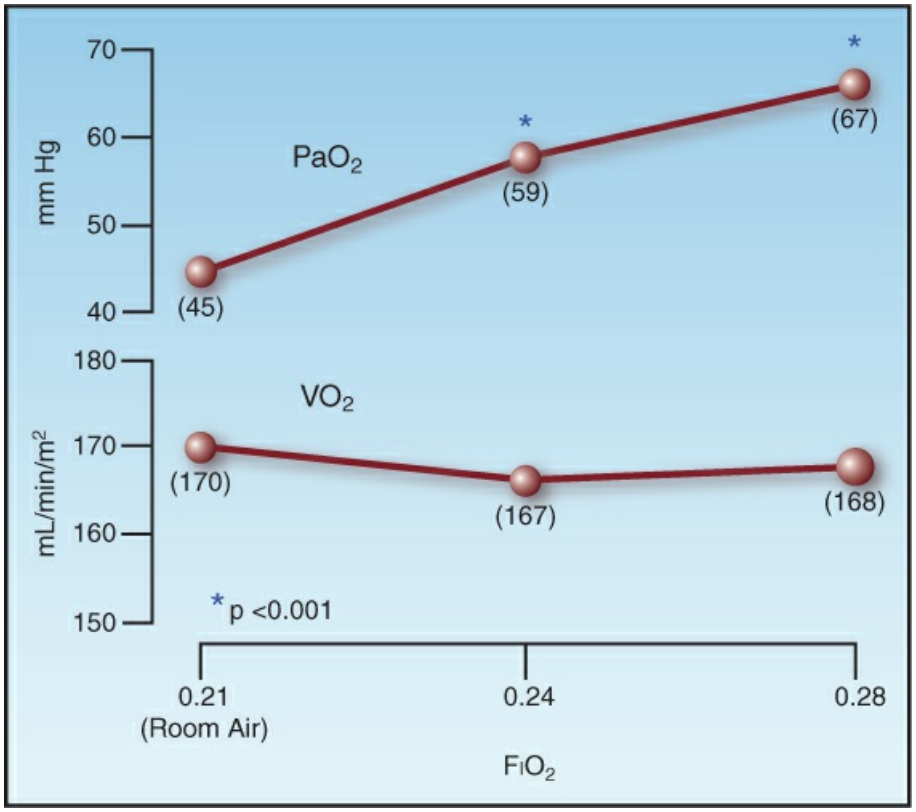

FIGURE 25.2 Results of a study in patients with severe hypoxemia showing that the increase in arterial PO_2 (PaO_2) from O_2 therapy is not accompanied by an increase in aerobic metabolism (VO_2). Numbers in parentheses are the mean values for each measurement. FIO_2 = fraction of O_2 in inhaled gas. Data from Reference 8.

Oxygen as a Vasoconstrictor

Oxygen acts as a vasoconstrictor in all major organs except the lungs (11), where it acts as a vasodilator. The principal mechanism for the vasoconstriction is loss of the vasodilating actions of nitric oxide, which is oxidized by one of the oxygen metabolites, the superoxide radical (see later) (12). This vasoconstriction has the following consequences:

. Oxygen promotes vasoconstriction in the coronary arteries, and can decrease coronary blood flow in patients with coronary artery disease (13).

. Oxygen-induced systemic vasoconstriction can decrease the cardiac output and promote tissue hypoperfusion, and this effect counteracts the ability of O_2 inhalation to increase systemic O_2 delivery (14).

. In animal studies, oxygen can completely obliterate capillary networks in skeletal muscle (15).

Implications

The observation that O_2 inhalation does not promote aerobic metabolism is consistent with the notion that the clinical use of O_2 is not based on tissue O_2 needs. Furthermore, *oxygen-induced vasoconstriction can be viewed as an inherent mechanism that protects the tissues from excess (unwanted) oxygen*. In other words, the tissues have enough O_2, and they don't want anymore.

OXYGEN DELIVERY SYSTEMS

A variety of oxygen delivery systems are available for spontaneously breathing patients, and the major ones are listed in Table 25.2, along with some characteristic features of each.

Flow Rate and F_IO_2

Supplemental O_2 is provided as a pure gas that is delivered into the mouth or nasopharynx at a preselected flow rate, and the fractional concentration of inhaled O_2 (F_IO_2) is determined by the balance between the rate of O_2 delivery and the patient's inspiratory flow rate. (There are some exceptions to this, as described later.) If the patient's inspiratory flow rate exceeds the rate of O_2 delivery, the excess flow will draw in room air, which will decrease the F_IO_2. A normal inspiratory flow rate is about 15 L/min (0.25 L/sec) during quiet breathing, but it can be as high as 120 L/min in patients with acute respiratory failure (16). Therefore, low-flow O_2 delivery systems (which have delivery rates below 15 L/min) are usually inadequate for patients with acute respiratory failure, especially those with respiratory distress or labored breathing.

Low-Flow Systems

Low-flow systems deliver O_2 at rates of ≤15 L/min, and are most suitable for patients with mild hypoxemia and no respiratory distress.

Low-Flow Nasal O_2

Low flow O_2 is typically delivered via nasal prongs at flow rates of 1–6 L/min (although rates up to 15 L/min are possible with large-bore nasal cannulas). The O_2 is usually humidified when the flow rate exceeds 4 L/min. The F_IO_2 during quiet breathing is about 24% (at 1 L/min) up to 40% (at 6 L/min).

The major advantages of low-flow nasal O_2 are simplicity of use and patient acceptance, including the ability for patients to eat and converse. The major disadvantage is the inability to achieve high concentrations of inhaled O_2.

Standard Face Masks

Standard face masks deliver oxygen at flow rates between 5 and 10 L/min (a minimum flow rate of 5 L/min is needed to clear exhaled gas from the mask). Exhalation ports on the side of the face mask also allow room air to be inhaled. This system can achieve a maximum F_IO_2 of about 60% during quiet breathing. Although face masks can deliver a slightly higher F_IO_2 than nasal prongs, they are more confining, and they do not permit oral feeding.

TABLE 25.2	Oxygen Delivery Systems		
System or Device	**Flow Rates**	**FIO_2 Range**	**Comments**
Low-Flow Nasal O_2	1–6 L/min	24–40%	Used for mild hypoxemia with no respiratory distress.
Standard Face Mask	5–10 L/min	35–50%	Same as above.
Non-Rebreather Mask	≥10 L/min	60–80%	Used for high O_2 requirements, but no longer favored.
Air-Entrainment Mask	2–15 L/min	24–50%	Designed for controlled O_2 delivery.
OxyMask™	1–≥15 L/min	24–90%	Can deliver high O_2 concentrations at relatively low flow rates.
High-Flow Nasal O_2	1–60 L/min	24–100%	Most effective system for severe hypoxemia and respiratory distress.

High-Flow Systems

High-flow systems include reservoir masks, air-entrainment devices, specialized "diffuser" masks (OxyMask™), and high-flow nasal O_2. These systems are intended for patients with high O_2 requirements and high ventilatory demands.

Reservoir Masks

Reservoir masks are standard face masks that are attached to a reservoir bag that is filled with oxygen from a constant-flow oxygen source. If the reservoir bag is kept inflated, the patient will draw primarily from the gas in the bag, which allows for higher concentrations of inhaled oxygen.

An example of a reservoir mask is shown in Figure 25.3. This is a *non-rebreather mask*, which is designed to prevent rebreathing of exhaled CO_2. The reservoir bag is filled with oxygen, and a one way valve between the bag and the mask allows inhalation of O_2 from the bag, but prevents exhaled CO_2 from entering the bag. One-way flaps on the mask allow exhaled gas to escape, while preventing inhalation of ambient air. Non-rebreather masks can theoretically achieve an FIO_2 of 100%, but the maximum FIO_2 is closer to 80%, because of leaks around the mask and valve malfunction. (*Note:* There is also a *partial rebreather mask*, which allows some of the exhaled CO_2 to enter the reservoir bag, but these devices are rarely used.)

Non-rebreather masks were once a popular method for providing high concentrations of O_2, but they have fallen from favor because of problems with CO_2 rebreathing from faulty valves, and troublesome hypoxemia from inadequately filled reservoir bags.

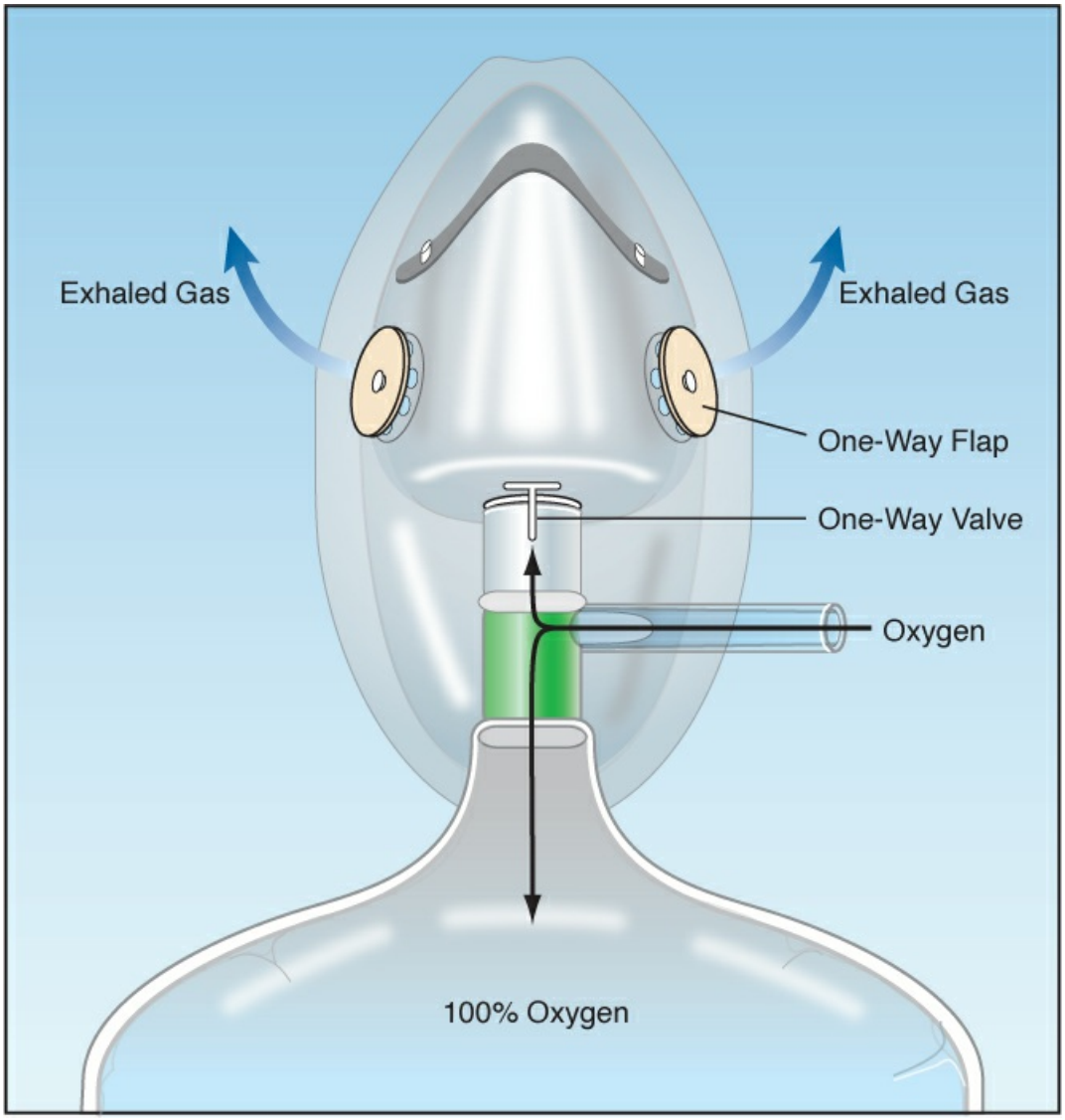

FIGURE 25.3 Non-rebreather mask. Oxygen is inhaled from the reservoir bag, and a one way valve prevents exhaled gas from entering the bag. Flaps on the mask allow exhaled gas to escape, while preventing inhalation of ambient air.

Air Entrainment Masks

Air entrainment masks are designed to deliver a constant F_IO_2. The operation of an air-entrainment device is shown in Figure 25.4 (17). The end of the oxygen inlet port is narrowed to create a high velocity stream of gas (analogous to the nozzle on a garden hose). This produces a shear force known as *viscous drag* that pulls room air into the device through air-entrainment ports. The greater the flow of O_2 into the mask, the greater the volume of air that is entrained, and this keeps the F_IO_2 constant. The F_IO_2 is varied by varying the size of the air entrainment ports. Although air-entrainment masks use O_2 flow rates of ≤15 L/min, they are considered high-flow systems because the total flow (i.e., O_2 flow plus room air flow) is often ≥60 L/min. The F_IO_2 range of these devices is 24 to 50%.

Air-entrainment masks have been popular for patients with chronic CO_2 retention, where an

inadvertent increase in F_IO_2 can lead to further increases in arterial PCO_2. However, their popularity has waned, because the continuous monitoring of arterial O_2 saturation with pulse oximetry is a deterrent to excessive oxygenation in patients with CO_2 retention.

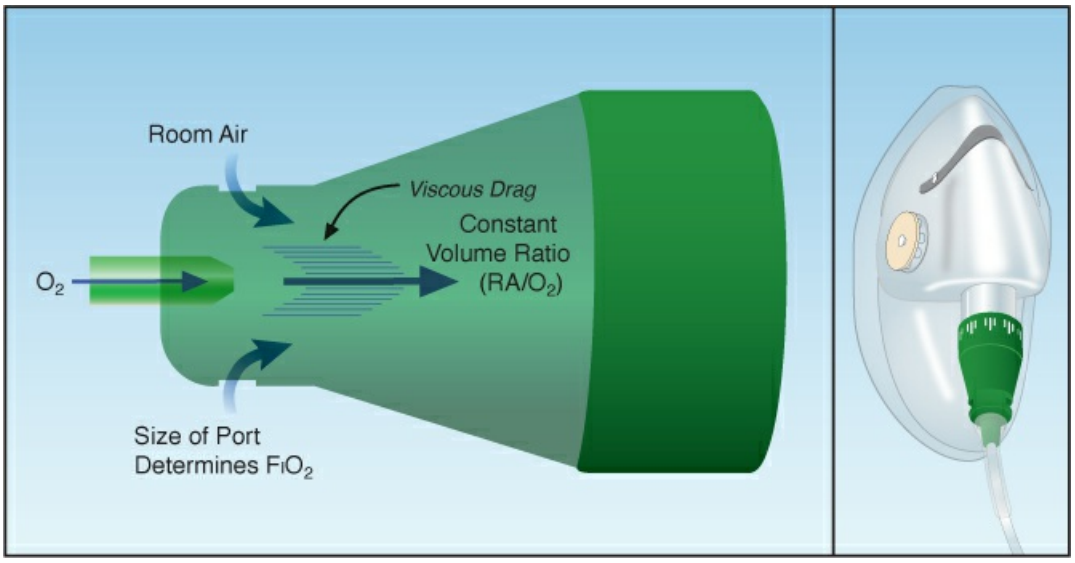

FIGURE 25.4 An air-entrainment device. A narrowing at the oxygen inlet creates a high-velocity stream of gas that creates viscous drag, which pulls in room air (RA). This "jet mixing" keeps the concentration of inhaled oxygen constant, regardless of changes in the flow rate of oxygen.

The OxyMask™

The Oxymask™ (Southmedic, Inc., Barrie, Ontario, Canada) is equipped with a proprietary device called a "diffuser" that delivers a concentrated stream of O_2 directly over the nose and mouth. This design allows for high concentrations of inhaled O_2 at relatively low flow rates (see Table 25.2). The mask also has large openings to facilitate the escape of exhaled CO_2.

The OxyMask has outperformed the non-rebreather mask (less CO_2 rebreathing) (18) and the air-entrainment mask (greater O_2 concentration at lower flows) (19). It is a superior mask for delivering high concentrations of O_2, at a relatively low cost (because of the low flow rate for O_2). However this mask otherwise offers no advantages over the high-flow nasal O_2 system described next.

High-Flow Nasal O_2

High-flow nasal O_2 (HFNO) is the greatest advance in O_2 delivery systems in recent memory. The basic design of the HFNO circuit is illustrated in Figure 25.5. This circuit provides heated and humidified gas for inhalation, and has an oxygen-air blender that allows titration of the F_IO_2 and flow rate independently. Flow rates of 40−60 L/min are achievable (depending on the manufacturer), and the nasal prongs have a tapered end to increase the velocity of flow (like the nozzle on a garden hose).

Physiological Benefits

HFNO has a number of beneficial effects, and these are listed in Table 25.3. The high flow rates,

combined with the increased velocity of flow from the design of the nasal prongs, results in a washout of the dead space in the nasopharynx (20,21). (*Note:* About 30% of a tidal volume is drawn from exhaled gas in the anatomical dead space.) This prevents rebreathing of exhaled CO_2, and also provides a "sink" that maintains the desired F_IO_2 if a patient overbreathes the flow rate for O_2 delivery. Surprisingly, HFNO also increases the end-expiratory lung volume, which, in turn, increases lung compliance (distensibility) and reduces the work of breathing (20,21).

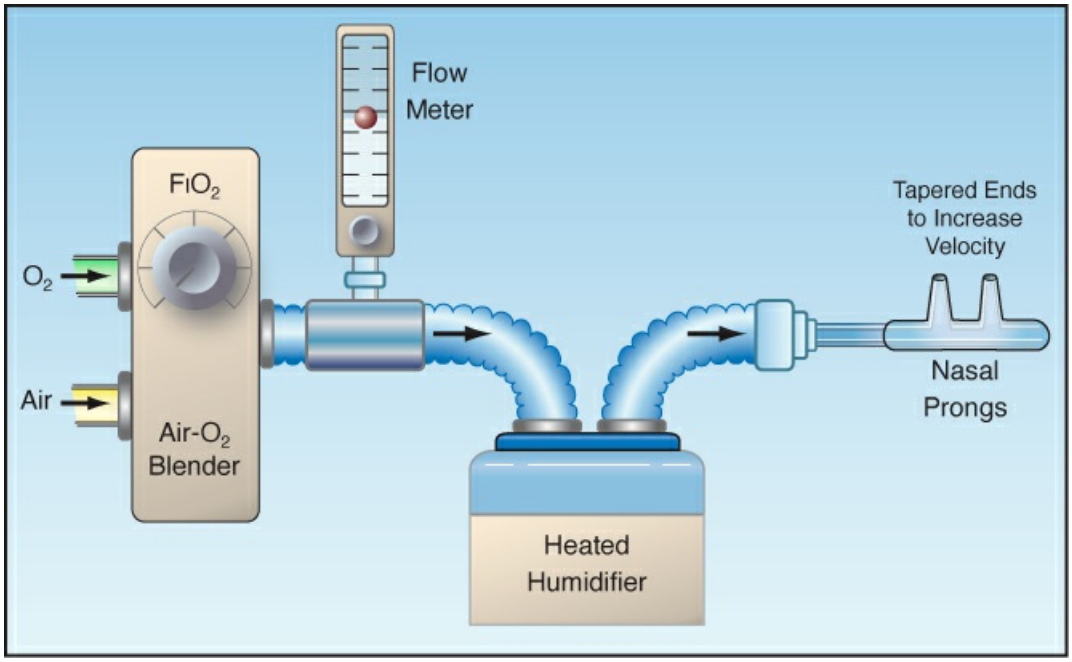

FIGURE 25.5 A schematic illustration of the circuit for high-flow nasal O_2. See text for explanation.

The ability of HFNO to increase the end-expiratory lung volume has been attributed to positive end-expiratory pressure (PEEP). However, HFNO can generate low-level PEEP (2–3 cm H_2O), but only with the mouth closed (22,23), which is a rare phenomenon in patients with acute respiratory failure.

TABLE 25.3 The Benefits of High-Flow Nasal Oxygen

Physiological	Clinical
• Reduces dead space • Increases end-expiratory lung volume • Increases lung distensibility • Reduces respiratory rate and minute ventilation • Reduces work of breathing	• Most effective O_2 delivery system for severe hypoxemia • Promotes comfortable breathing • Can reduce the risk of "patient self-induced lung injury" • Allows oral food intake • Can prevent intubation

Clinical Benefits

Other than the ability to correct severe hypoxemia, the principal benefit of HFNO is the tendency to alleviate respiratory distress and promote comfortable breathing. This not only promotes

patient comfort, it also reduces the risk of "patient self-induced injury", a form of lung injury produced by labored breathing, which is described in Chapter 24 (see Figure 24.4). This may explain why HFNO has reduced the rate of intubations in some studies (24), although this is not a consistent finding (25).

HFNO has traditionally been used when hypoxemia is refractory to conventional methods of O_2 inhalation, but the numerous benefits of HFNO has prompted a recommendation that HFNO should *replace* conventional O_2 therapy for patients with acute hypoxemic respiratory failure (26).

OXYGEN AS A SOURCE OF INJURY

The introduction to this chapter included a statement about protecting our food from the oxygen in atmospheric air (e.g., with vacuum sealing), and the reason is that *oxygen decomposes organic matter* by disrupting organic molecules (including carbohydrates, proteins, and lipids). The chemical derivatives of oxygen, which are called *reactive oxygen species* (ROS) are even more damaging than the parent molecule, and are capable of inflicting lethal cell injury (27). In fact, contrary to the popular perception that oxygen protects cells from injury in critically ill patients, the accumulating evidence indicates that *oxygen (via the production of ROS) is an important source of cell injury in critically ill patients* (27–29). (The role of ROS in inflammation is described in Chapter 17.) The following is a brief description of the injurious nature of oxygen.

Oxygen Metabolism

The metabolism of O_2 takes place at the end of the electron transport chain in mitochondria (within the cytochrome oxidase complex), where the electrons that accumulate in the process of ATP production are cleared by adding them to O_2 to produce water. (The addition of electrons to an atom or molecule is known as chemical reduction.) The O_2 molecule can accept four electrons, but only one electron can be added per reduction reaction (the reason for this is beyond the scope of this chapter), which results in the reaction sequence shown in Figure 25.6.

The intermediates in the reduction of O_2 to water include the superoxide radical, hydrogen peroxide, and the hydroxyl radical. All are reactive oxygen species (ROS) that are capable of disrupting and damaging vital cell components (e.g., membrane lipids, cytoplasmic proteins, and DNA) by the chemical process of *oxidation* (which removes electrons from a substrate). Thus, ROS are sometimes referred to as oxidizing agents, or *oxidants*. Some relevant features of the ROS generated by O_2 metabolism are summarized below (27).

- The superoxide and hydroxyl radicals are *free radicals* (i.e., they have an unpaired electron in their outer orbitals), and are highly reactive.
- Hydrogen peroxide is not a free radical, but it is a powerful oxidizing agent that readily moves across cell membranes, and can be widely distributed throughout the body.
- The hydroxyl radical is the most reactive molecule known in biochemistry, and enters into a reaction within three molecular diameters of its point of origin. It is the most destructive of all the ROS, and is a major source of oxidant-induced cell injury.

. Free iron in its reduced form (Fe^{++}) catalyzes the formation of the hydroxyl radical, and thus free iron can act as a pro-oxidant (see later).

Normally, at least 95% of oxygen is completely reduced to water, and only a very small fraction (about 3%) of O_2 metabolism generates damaging ROS (27). However, there is *a more important, source of ROS: i.e., the inflammatory response* (see next).

Neutrophil Activation

As described in Chapter 17 (see Figure 17.1), the activation of neutrophils involves a precipitous rise (up to 20-fold) in O_2 consumption (30), which is known as the *respiratory burst*, and is designed to generate ROS. Neutrophils also have a myeloperoxidase enzyme that generates *hypochlorite*, which is the active ingredient in household bleach.

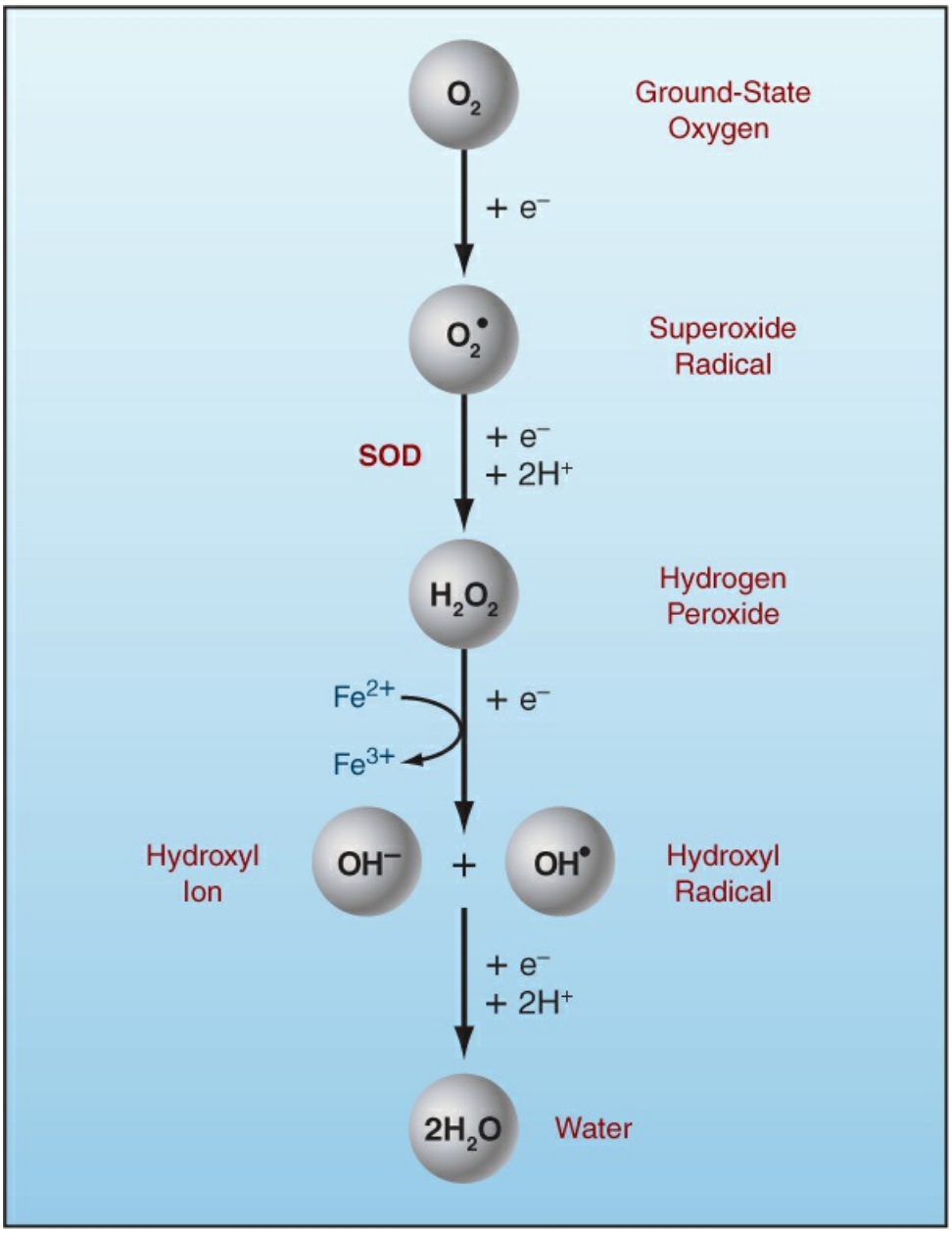

FIGURE 25.6 The reaction sequence for the chemical reduction of oxygen to water, which takes place at the end of the electron transport chain in mitochondria. Free radicals are indicated by a superscripted dot. See text for explanation.

Inflammatory Injury

There is abundant evidence that ROS have a prominent role in the tissue injury attributed to inflammation (see Chapter 17) (31). The damaging effects of ROS are accelerated by the *tendency for free radicals to create chain reactions* (32). When a free radical reacts with a non-radical, the non-radical loses an electron and is transformed into a free radical, which can then remove an electron from another nonradical to produce another free radical, and so on. This creates a self-sustaining reaction or *chain reaction*, and these reactions are troublesome because they continue after the inciting event is eliminated. (A fire is a familiar example of a chain

reaction involving free radicals.) Chain reactions would explain the progression of inflammatory multiorgan damage in severe sepsis and septic shock after the infection has been eradicated.

Antioxidant Protection

Oxidative (oxygen-related) injury is kept in check by a vast array of endogenous *antioxidants* (i.e., atoms or molecules that prevent or block the actions of oxidizing agents). The following is a brief description of the major antioxidants, and Figure 25.7 shows their mechanisms of action.

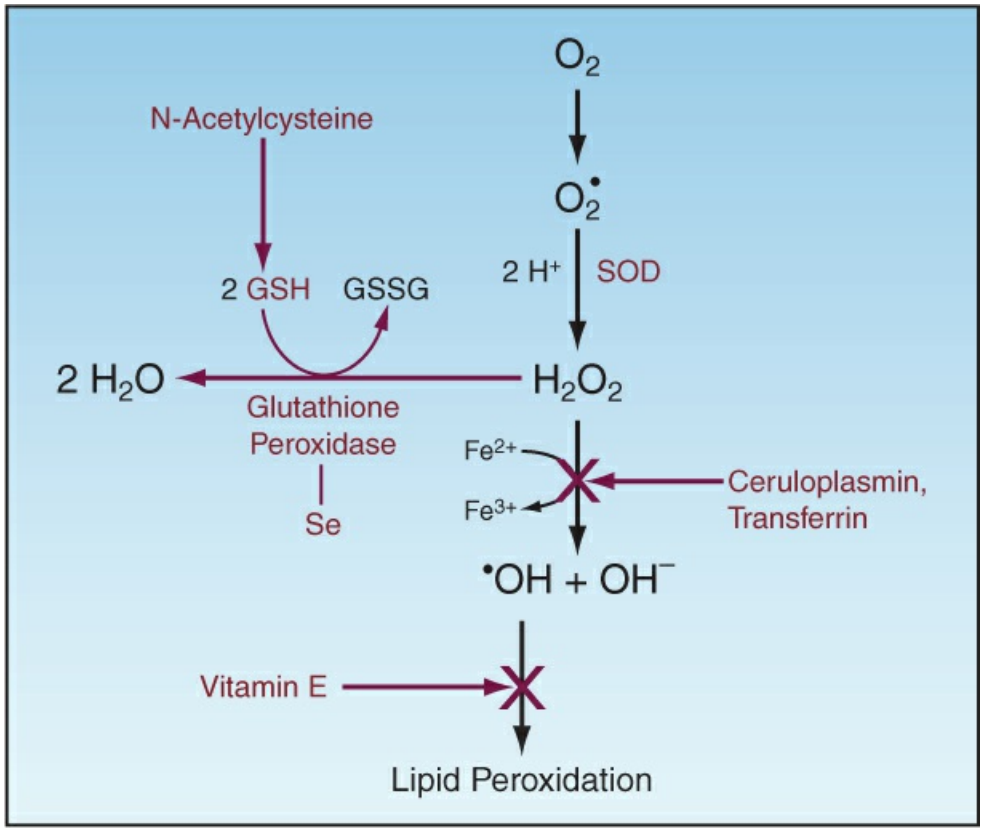

FIGURE 25.7 The actions of some endogenous and exogenous antioxidants (shown in red). SOD = superoxide dismutase, GSH = reduced glutathione, GSSG = oxidized glutathione, Se = selenium. See text for explanation.

Superoxide Dismutase

Superoxide dismutase (SOD) is an enzyme that facilitates the conversion of superoxide radicals to hydrogen peroxide. SOD is considered an antioxidant because it clears the superoxide radical, but it also increases the production of hydrogen peroxide, and thus it can also act as a pro-oxidant (33).

The role of SOD in inflammatory injury is suggested by animal studies of pain perception, which have shown that treatment with an SOD mimetic curtails the pain response to inflammation (34). This implicates superoxide radicals as a source of inflammatory pain; a notion that is supported by evidence that SOD is inactivated by products of inflammation (35). These findings have important implications for the development of nonopioid analgesics for painful inflammation.

Glutathione

Glutathione is a sulfur-containing tripeptide that is considered *the major intracellular antioxidant in the human body* (36,37). In its reduced form, glutathione (GSH in Figure 25.7) donates electrons to reduce hydrogen peroxide to water in a reaction that is catalyzed by a selenium-dependent enzyme, glutathione peroxidase:

$$H_2O_2 + 2\ GSH \rightarrow 2\ H_2O + GSSG \qquad (25.2)$$

Glutathione is present in high concentrations is most mammalian cells, and is synthesized *de novo* within cells. It can be exported extracellularly, but plasma levels are three orders of magnitude lower than intracellular levels (38). Glutathione levels in lung lavage fluid are 140-fold higher than plasma (39), suggesting that glutathione plays an important role in protecting the lung from oxidant injury. There is evidence that *glutathione is depleted in critically ill patients* (40).

N-ACETYLCYSTEINE: Glutathione does not move readily into cells, and exogenous glutathione administration has little effect on intracellular levels (41). However, the popular mucolytic agent *N-acetylcysteine* is a glutathione analogue that can cross cell membranes and serve as a glutathione surrogate (as proven by the beneficial effects of N-acetylcysteine in acetaminophen toxicity, which is attributed to glutathione deficiency - see Chapter 52). N-acetylcysteine has a promising future as an antioxidant in critically ill patients (42).

SELENIUM: Selenium is an essential trace element that serves as a cofactor for the glutathione peroxidase enzyme in humans. The recommended dietary allowance (RDA) for selenium is 55 µg daily in adult men and women (43). The absence of dietary selenium produces measurable decreases in glutathione peroxidase activity after just one week (44). Selenium levels in blood are typically low in critically ill patients (45), and high-dose selenium replacement (1000 µg IV daily) has been associated with improved survival in patients with severe sepsis and septic shock (45).

Selenium status can be monitored using whole blood selenium (normal range = 0.96–1.78 µmol/L) or serum selenium (normal range = 0.72–1.33 µmol/L). If needed, selenium can be given intravenously as sodium selenite. The highest dose that is considered safe is 200 µg daily.

Vitamin E

Vitamin E (alpha-tocopherol) is a lipid-soluble vitamin that is found in the interior of most cell membranes, where it serves as a "chain breaking" antioxidant to halt the progression of lipid peroxidation (i.e., the oxidation of polyunsaturated fatty acids, also known as *rancidity* when it occurs in food products), which proceeds as a chain reaction. To accomplish this, vitamin E donates an electron to a free radical intermediate in lipid peroxidation, and in so doing, vitamin E becomes a free radical, but an innocuous one. This reaction halts the chain reaction of lipid peroxidation. (*Note:* Lipid peroxidation is initiated by the hydroxyl radical, and Figure 25.7 shows Vitamin E blocking this reaction, to indicate that Vitamin E blocks lipid peroxidation.)

Vitamin E depletion has been reported in patients with acute respiratory distress syndrome (46), and there is evidence that high-dose vitamin E has beneficial effects in trauma victims (see later). The normal concentration of vitamin E in plasma is 1 mg/dL, and a level below 0.5 mg/dL

is evidence of deficiency (47).

Vitamin C

Vitamin C (ascorbic acid) is a water-soluble vitamin that is best known for its essential role in collagen formation. However, it is also a reducing agent that can donate electrons to free radicals to erase their adverse effects. As a result, ascorbate can act as a "scavenger" for oxygen-derived free radicals: i.e., superoxide radicals and hydroxyl radicals (48). Ascorbate also donates electrons to regenerate Vitamin E from the inactive Vitamin E radical.

Ceruloplasmin and Transferrin

Ceruloplasmin and transferrin account for most of the antioxidant activity in plasma (49). The antioxidant activity of both proteins is related to their actions in limiting free iron in the reduced form (Fe^{2+}), which will limit the production of hydroxyl radicals. Ceruloplasmin oxidizes iron from the Fe^{2+} to the Fe^{3+} state, and transferrin binds iron in the oxidized or Fe^{3+} state. The role of free iron as a pro-oxidant (50) may explain why most of the iron in the body is bound to proteins or sequestered (e.g., in the bone marrow).

Oxidative Stress

The risk of oxidative tissue injury is determined by the balance between oxidant and antioxidant activities. When oxidant activity exceeds the neutralizing capacity of the antioxidants, the excess or unopposed oxidant activity can promote tissue injury. This condition of *unopposed biological oxidation is known as oxidative stress*, and it is the principal source of oxidative tissue injury. The most familiar example of oxidative stress is severe or persistent inflammation, especially in critically ill patients, which combines an increase in production of oxidants (ROS) with likely depletion of antioxidants.

Monitoring oxidative stress has obvious benefits for the care of critically ill patients (or any patient with inflammatory tissue injury). One promising method involves the measurement of lipid peroxidation products in exhaled gas (51), but this methodology is not currently available in clinical practice.

PULMONARY OXYGEN TOXICITY

Pulmonary oxygen toxicity is an inflammatory lung injury (similar to the acute respiratory distress syndrome described in Chapter 24) that occurs in response to the prolonged inhalation of high concentrations of oxygen. The following are some relevant issues regarding this form of oxidative injury.

Species Differences

The tendency to develop pulmonary oxygen toxicity varies in different species. For example, laboratory rats will die of respiratory failure after 5 to 7 days of breathing 100% O_2, while cold-blooded species like sea turtles can breathe pure O_2 for several weeks and even months without harm (52). Non-human primates, which are closest to humans, show signs of pulmonary O_2 toxicity after about one week of breathing pure oxygen (53).

Human Studies

In healthy volunteers, inhalation of 100% O_2 for 6 to 12 hours results in a tracheobronchitis and a decrease in vital capacity attributed to absorption atelectasis (54). Prolonged exposure to 100% O_2 has been reported in only 6 humans: 5 with irreversible coma who received 100% O_2 for 3 to 4 days (55), and one healthy volunteer who inhaled pure O_2 for 4.5 days (56). In all these cases, the subjects developed a pulmonary condition that was consistent with inflammatory lung injury.

What F_IO_2 is Toxic?

Based on the observation of a decreased vital capacity when the F_IO_2 exceeds 60% (54), the threshold F_IO_2 for pulmonary O_2 toxicity was set at 60%. However, adopting a single threshold F_IO_2 for all patients neglects the contribution of endogenous antioxidants to the risk of oxygen toxicity. For example, animal studies have shown that pulmonary O_2 toxicity is exacerbated by vitamin E deficiency (57) and glutathione deficiency (58). *Since antioxidant depletion seems to be common in ICU patients* (40,45,46), *it is reasonable to assume that the toxic level of* F_IO_2 *is much lower than suspected* in critically ill patients. Therefore, the best practice is keeping the F_IO_2 at the lowest tolerable level.

Promoting Antioxidant Protection

Another approach to minimizing the risk of pulmonary O_2 toxicity (and any source of oxidative cell injury) is to monitor and correct antioxidant levels. This approach is supported by evidence of antioxidant depletion in critically ill patients (40,45,46) Evidence of benefit from such an approach is provided by a study in trauma patients (59), which showed that a high-dose antioxidant cocktail of vitamin C (1000 mg every 8 hrs), vitamin E (1000 units every 8 hrs) and selenium (200 µg daily) for 7 days was associated with a significant decline in cases of respiratory failure and ventilator dependence. Promoting antioxidant protection for your patients is similar to the use of tightly sealed plastic containers to protect your food.

A FINAL WORD

Why is Oxygen a Vasoconstrictor?

For those who like to consider teleology in biological design, the actions of oxygen to promote systemic vasoconstriction merits some attention.

The ability of inhaled O_2 to augment tissue oxygenation is determined by its influence on both the O_2 content in arterial blood (CaO_2), and the cardiac output (CO), as defined by the equation for arterial O_2 delivery: i.e.,

$$O_2 \text{ Delivery} = CaO_2 \times CO \qquad (25.3)$$

Inhaled O_2 will increase the CaO_2, but the O_2-induced systemic vasoconstriction leads to a decrease in CO, and the net effect is that O_2 delivery remains unchanged (60). This would explain why O_2 inhalation has no effect on aerobic metabolism, as shown in Figure 25.2.

The vasoconstrictor response to O_2 can then be viewed as a defense mechanism that is designed to protect the tissues from excess oxygen (i.e., more than is needed to maintain aerobic metabolism). This will limit the risk of oxidative tissue injury, and in this sense, *the vasoconstrictor response to O_2 can be viewed as an antioxidant defense mechanism.*

The human body seems designed to protect the vital organs from oxygen, and *our liberal use of oxygen is the contrary to human design.*

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Chapter 26

Noninvasive Ventilation

We…repeatedly enlarge our instrumentalities without improving our purpose.

Will Durant (*a*)

Noninvasive positive pressure breathing was introduced in the 1940s (about a decade before conventional mechanical ventilation), but it was delivered through a mouthpiece, and could only be used for brief periods of time (10–15 minutes) (1). For the next 40 years, this method of "intermittent positive pressure breathing" (IPPB) was used for delivering inhaled bronchodilators, and for the prevention of postoperative atelectasis. The use of "continuous positive airway pressure" (CPAP) was introduced in the early 1980s, and rapidly gained traction as a treatment for obstructive sleep apnea (2). This led to improvements in mask design, and by the 1990s, reports began to appear about the use of positive pressure breathing through face masks to manage patients with acute respiratory failure (3). Since that time, the popularity of *noninvasive ventilation* has skyrocketed, but the benefits have been variable (as described in this chapter).

This chapter describes the fundamentals of using noninvasive ventilation, including what to use, what to monitor, and what to expect in different types of acute respiratory failure (4). The last section describes the effects of positive pressure breathing on cardiac performance.

METHODS OF NONINVASIVE VENTILATION

The following is a description of the principal methods of pressure-assisted breathing that do not require endotracheal intubation.

Continuous Positive Airway Pressure

During normal breathing, the descent of the diaphragm creates a negative intrathoracic pressure that draws air into the lungs, and exhalation proceeds passively until the intrathoracic pressure returns to atmospheric (zero reference) pressure). When breathing with "continuous positive airway pressure" (CPAP), the pressure at the end of expiration is positive relative to atmospheric pressure, and the positive pressure is maintained through the respiratory cycle. This is

demonstrated in Figure 26.1, which shows a spontaneous breathing pattern with a positive end-expiratory pressure of 5 cm H_2O.

The positive pressure in CPAP is created by a constant flow of air or oxygen that is adjusted to achieve the desired pressure level (usually 5–10 cm H_2O). This pressure helps to prevent collapse of the small airways and alveoli at the end of expiration, and increases the end-expiratory lung volume (i.e., the functional residual capacity), but it does not augment the tidal volume.

Clinical Uses

The principal use of CPAP is in patients with obstructive sleep apnea, where the positive pressure prevents the inspiratory collapse of the pharynx that causes the obstruction to airflow (5). CPAP has also been successful in managing patients with acute cardiogenic pulmonary edema (6), for reasons described later in the chapter. Overall, CPAP provides only limited pressure support, and it is rarely used to manage patients with acute respiratory failure.

Bi-Level Positive Airway Pressure

Noninvasive ventilation is typically a patient-triggered, pressure-targeted mode of ventilation that provides pressure-augmented tidal volumes along with positive end-expiratory pressure (PEEP) (7). This is illustrated in Figure 26.1. The patient triggers each positive-pressure lung inflation (indicated by the negative pressure swings), and the inspiratory pressure gradually rises until it reaches a pre-selected pressure. Exhalation then proceeds until the pressure reaches a pre-selected positive end-expiratory pressure (PEEP). Peak inspiratory pressures are typically 10–20 cm H_2O, and PEEP levels are usually 5–10 cm H_2O. Higher pressure are generally not advised because they are poorly tolerated by patients, and they promote leaks around the face mask.
(Note: The mode of ventilation just described is typically called *bi-level positive airway pressure*, or simply *BiPAP, however* this is a proprietary name (registered as a trademark name by Philips Respironics), and is used sparingly in this chapter.

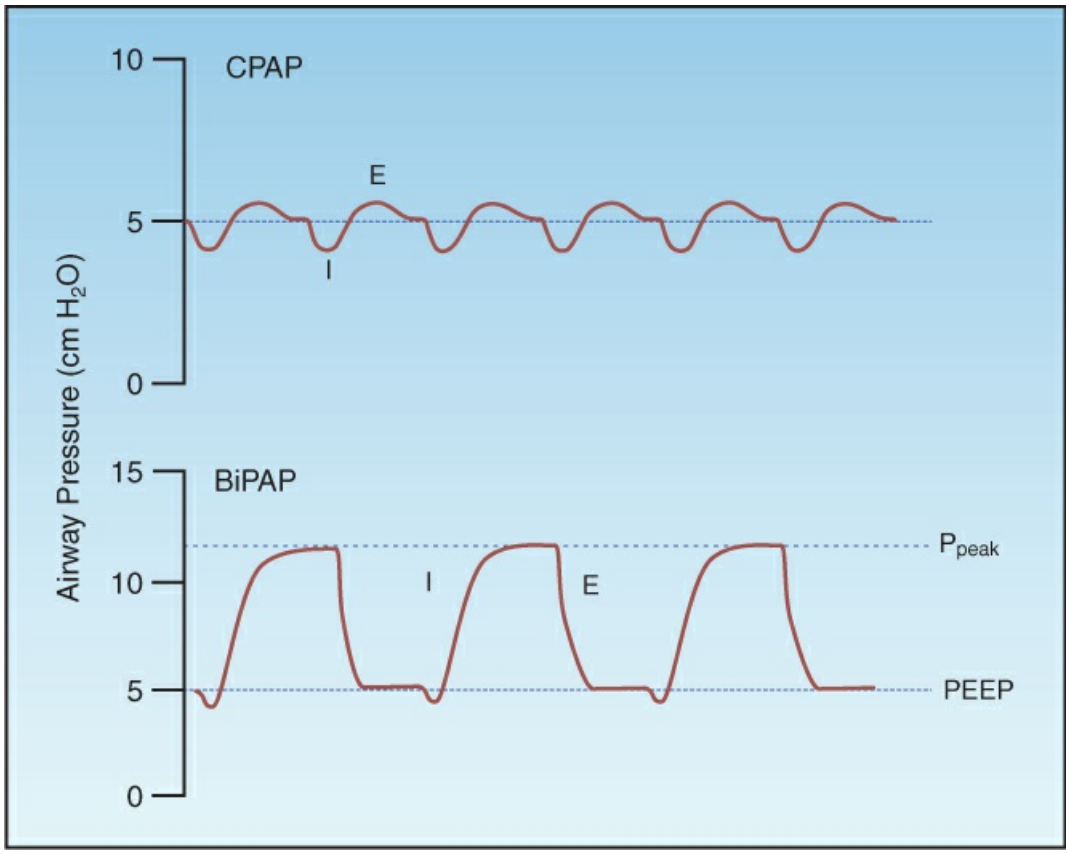

FIGURE 26.1 Airway pressure waveforms for continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP). See text for explanation.

Pressure Support Ventilation

Pressure support ventilation (PSV) is an interactive form of pressure-targeted ventilation that adjusts the ventilator breath to the ventilatory demands of the patient (7,8). This is explained using the pressure waveform in Figure 26.2. The following statements correspond to the numbers located at different points on the waveform.

. PSV is a patient-triggered mode of ventilation, and the initial negative pressure deflection represents the spontaneous inspiratory effort that triggers the ventilator breath.

. Once the ventilator breath is triggered, high flow rates are used to produce a rapid rise in airway pressure, in order to reach the desired inspiratory pressure as soon as possible.

. When the desired pressure level is achieved, it is kept constant by servo-adjusting the ventilator flow rate to the inspiratory flow demands of the patient.

. The lung inflation is terminated when the patient's inspiratory flow rate drops to 25% of the peak flow.

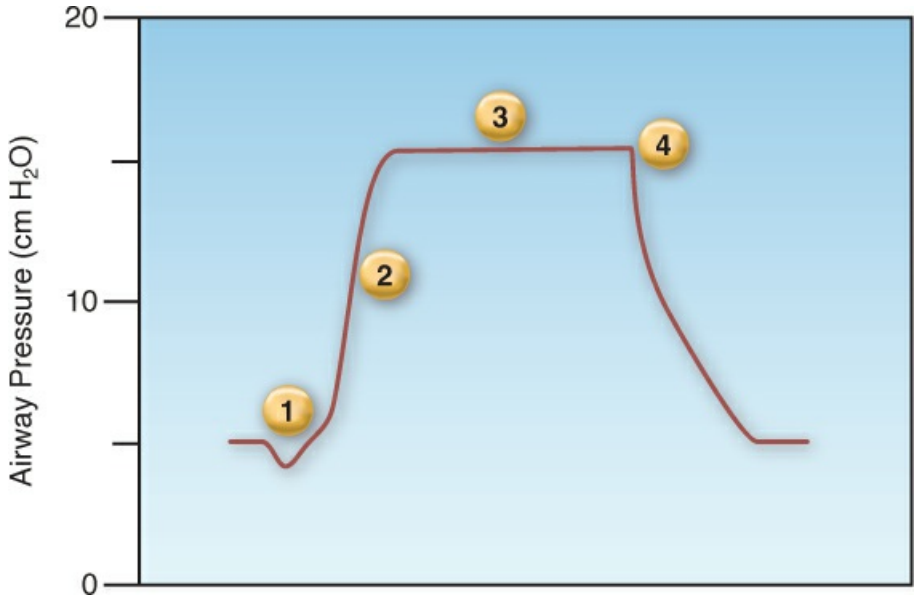

FIGURE 26.2 The pressure waveform in pressure support ventilation (PSV). The numbers at different points on the waveform are explained in the text.

This interaction allows the patient to determine the inflation time and tidal volume, which promotes patient-ventilator synchrony, and reduces the work of breathing (8). PSV is typically reserved for cases of patient-ventilator asynchrony, and is also popular for spontaneous breathing trials used in the process of weaning patients from mechanical ventilation (see Chapter 30).

Proportional Assist Ventilation

Proportional assist ventilation (PAV) is another interactive form of noninvasive ventilation that adjusts the peak inspiratory pressure to the patient's work of breathing (10). This is accomplished by periodic measurements of respiratory mechanics (i.e., compliance and resistance), which are carried out (in a proprietary fashion) by ventilators capable of delivering PAV. There is no evidence that PAV is superior to PSV as a mode of noninvasive ventilation (11).

Face Masks

The emergence of noninvasive ventilation is largely due to advances in the design of the mask interface. Low-level CPAP can be delivered by nasal masks, but full face masks are required for BiPAP, and the face masks must be tight-fitting to minimize leaks (although most BiPAP machines can compensate for mask leaks). These face masks are uncomfortable (see Figure 26.3), and are poorly tolerated by patients. In addition to general discomfort, masks can cause skin breakdown at points of contact, especially on the bridge of the nose. "Mask intolerance" is a significant source of failed attempts to prevent intubation with noninvasive ventilation. In one study, 18% of the noninvasive ventilation failures were attributed to mask intolerance (12).

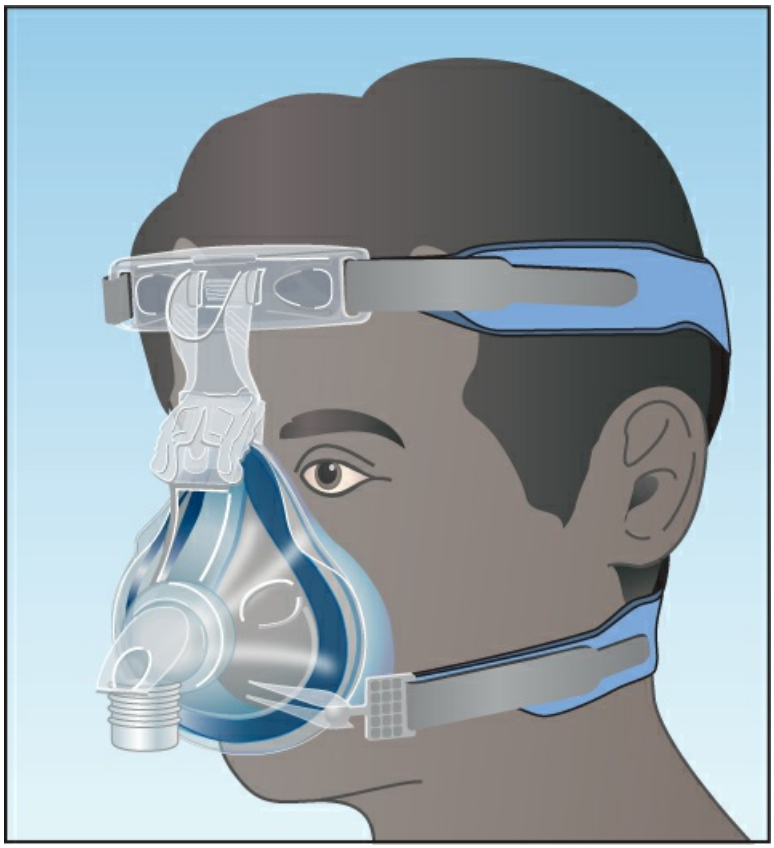

FIGURE 26.3 A tightly-secured face mask used for noninvasive ventilation.

The Helmet

An alternative to the tight-fitting face masks is available with a device called a "helmet", which is a transparent hood that encloses the entire head, and has a soft collar that provides a seal at the neck. Studies comparing helmets and face masks have shown fewer intubations and even fewer deaths with the use of helmets (13). However, these devices are rarely used in adults.

USING NONINVASIVE VENTILATION

The utility and success of noninvasive ventilation (NIV) is determined by several factors, including the type of patient, the type and severity of illness, and the type of respiratory failure.

Type of Patient

The patient selection criteria for NIV are presented as a checklist in Table 26.1. As a general rule, all patients with acute respiratory failure are candidates for NIV if the following criteria are satisfied: (a) the acute respiratory failure is not an immediate threat to life, (b) there is no life-threatening circulatory collapse, (c) the patient is awake or arousable, and is cooperative, (d) there are no persistent or recurrent seizures, (e) there is no hematemesis or persistent vomiting, and (f) there is no obstruction that will prevent effective ventilatory support through a face mask (e.g., laryngeal mass or edema). These criteria do not apply to patients who refuse intubation and mechanical ventilation, which has been reported in 20% of patients receiving NIV (14).

TABLE 26.1 Checklist for Noninvasive Ventilation

Are any of the following conditions present in a patient who presents with acute respiratory failure ?

	YES	NO
1. Agonal breathing.	☐	☑
2. Life-threatening circulatory collapse.	☐	☑
3. Severe agitation or uncontrolled seizures.	☐	☑
4. An acute confusional state.	☐	☑
5. Coma with inadequate airway protection.	☐	☑
6. Hematemesis or persistent vomiting	☐	☑

If the answer is NO to all of the above, the patient is a candidate for noninvasive ventilation.

NIV is a consideration in any case of acute respiratory failure that does not meet the criteria in Table 26.1. However, *the likelihood of success* (i.e., preventing intubation) *is dependent on the type of respiratory failure* (i.e., hypercapnic or purely hypoxemic respiratory failure), *and the underlying illness* (see next).

Hypercapnic Respiratory Failure

The most successful use of NIV is in patients with acute hypercapnic respiratory failure from an acute exacerbation of COPD (15). The benefits of NIV in this condition are shown in Figure 26.4. The graphs in this figure display the averaged results of 17 clinical studies, and they show that NIV drastically reduces the intubation rate, and has a smaller but significant survival benefit (15). As a result, *noninvasive ventilation is recommended as a first-line therapy for acute exacerbations of COPD that are associated with acute hypercapnic respiratory failure* (4). NIV does not have this benefit when the hypercapnia is chronic (4).

Evaluating the Response

About 10–20% of COPD patients with acute hypercapnia will not respond favorably to NIV (15,16). These patients can be identified by checking the $PaCO_2$ after one hour of NIV, and comparing it to the baseline $PaCO_2$. *Failure of the $PaCO_2$ to decrease significantly (e.g., by at least 10%) after one hour of NIV is evidence of a poor response; i.e., NIV failure* (16). Altered mentation (e.g., from hypercapnia) can take longer to resolve (17), and should not be used as an early indication of NIV failure.

There is a reluctance to intubate patients with advanced COPD (because of the fear that mechanical ventilation will be a permanent condition), but delays to intubation can also have adverse consequences, and intubation should be a serious consideration at first evidence of NIV failure.

Obesity Hypoventilation Syndrome

Despite a paucity of studies, the available evidence shows that NIV is effective in reducing the intubation rate in patients with acute hypercapnic respiratory failure from the obesity hypoventilation syndrome (18). It seems reasonable to assume that the one-hour $PaCO_2$ evaluation just described is also valid for this condition.

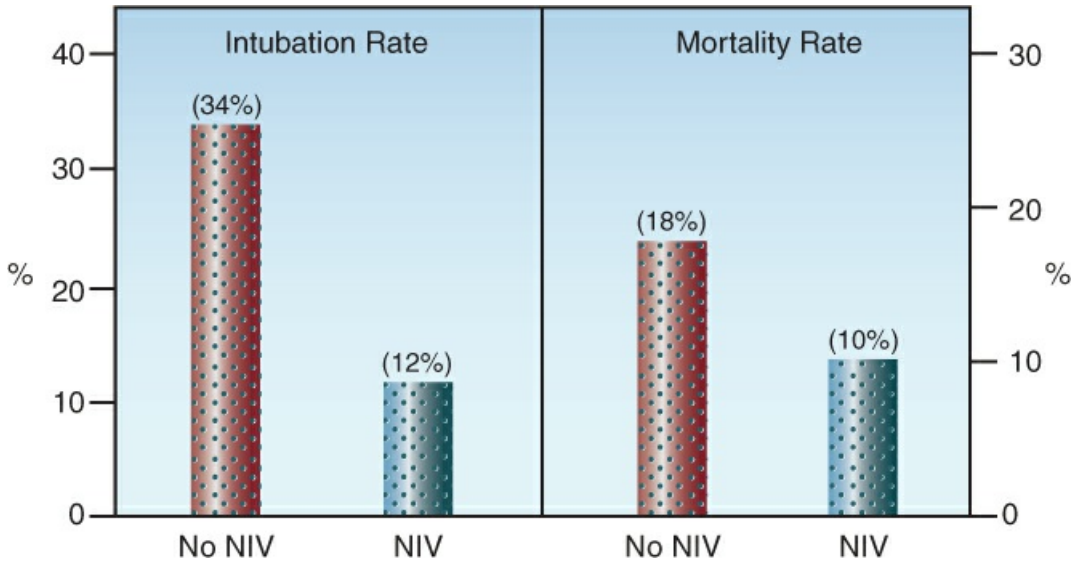

FIGURE 26.4 The effects of noninvasive ventilation on intubation rate and mortality rate in patients with acute exacerbation of COPD and hypercapnic respiratory failure. Data represents the pooled results from 17 clinical studies. From Reference 14.

Hypoxemic Respiratory Failure

The success of NIV in hypoxemic respiratory failure is dependent on the underlying condition. This is demonstrated in Figure 26.5, which shows the frequency of NIV failure in a variety of conditions that produce hypoxemic respiratory failure (19–21). The failure rate is lowest in cardiogenic pulmonary edema, and highest in community-acquired pneumonia. In the acute respiratory distress syndrome (ARDS), the likelihood of failure is dependent on the severity of illness (see also Figure 24.5) (20).

Evaluating the Response

Observations from clinical studies have shown that *failure to increase the PaO_2/FIO_2 ratio after one hour of NIV is evidence of a poor response; i.e., NIV failure* (19). This should be an indication for intubation if the hypoxemia is severe, or the underlying illness has a high failure rate for NIV.

Cardiogenic Pulmonary Edema

Both CPAP and NIV are highly successful (and equally effective) in cardiogenic pulmonary edema (22). This benefit is not limited to improvements in lung function, because *positive intrathoracic pressure can increase cardiac stroke output* (23,24). This is illustrated in Figure 26.6, which shows the changes in arterial pressure that occur during a positive pressure lung inflation. The positive airway (intrathoracic) pressure is accompanied by a steady rise in arterial pressure, which subsides as the pressure returns to baseline. The shaded areas in the arterial pressure waveforms (which are proportional to stroke volume) show that the increase in arterial pressure is a reflection of an increase in cardiac stroke output. This figure demonstrates that positive intrathoracic pressure increases the stroke output of the left ventricle. This effect is due to a decrease in left ventricular afterload (25), which is explained in the upcoming section on cardiac performance. (*Note:* The respiratory changes in stroke volume during mechanical ventilation can be used to evaluate fluid responsiveness, as shown in Figure 11.5).

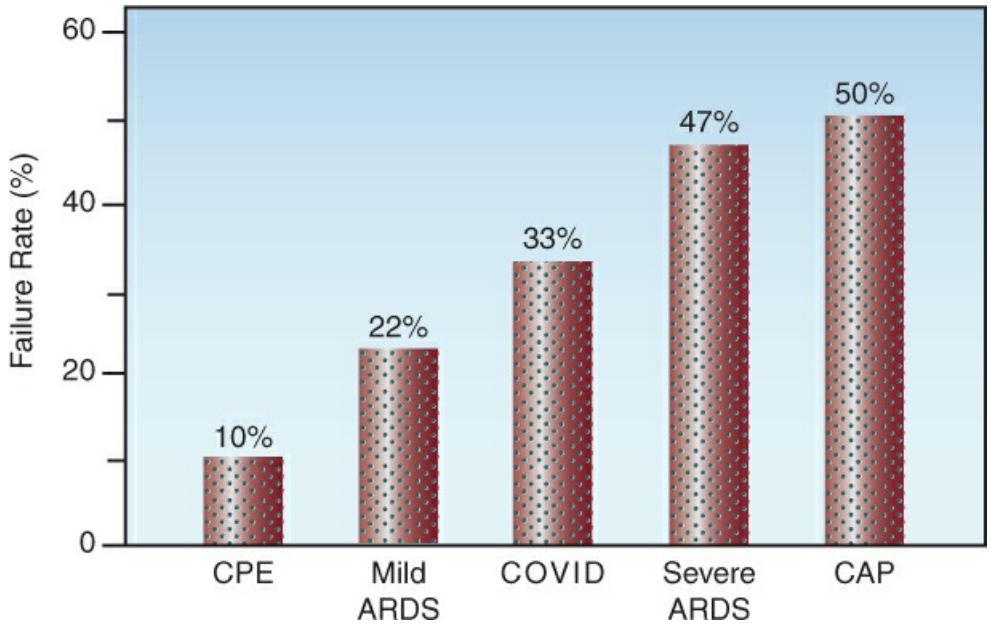

FIGURE 26.5 The failure rate of noninvasive ventilation in common conditions that cause acute hypoxemic respiratory failure. CPE = cardiogenic pulmonary edema, ARDS = acute respiratory distress syndrome, CAP = community acquired pneumonia. Data from References 19–21.

The Role of High-Flow Oxygen

High-flow nasal oxygen (HFNO), which is described in Chapter 25, is traditionally used for cases of hypoxemic respiratory failure when the hypoxemia is refractory to conventional methods of O_2 inhalation. However, HFNO has beneficial effects other than oxygenation, including an increase in lung compliance (distensibility), a decrease in the work of breathing, and a decrease in labored breathing (see Table 25.3) (26,27). These added benefits (which are attributed to the high flow rates) make HFNO a potential alternative to NIV for patients with hypoxemic respiratory failure, and this has been validated in studies showing equivalent intubation rates with HFNO and NIV in patients with acute hypoxemic respiratory failure (28). In addition, there is evidence that HFNO is superior to NIV for preventing intubation in immunocompromised patients (29).

The overall evidence indicates that *HFNO is equivalent to NIV for preventing intubation in*

patients with acute hypoxemic respiratory failure, and it may be more effective than NIV in immunocompromised patients. Considering that HFNO avoids the use of face masks, and thus is more comfortable for patients, while also allowing the oral intake of food and medications, it seems that HFNO should be preferred to NIV for patients with acute hypoxemic respiratory failure.

CARDIAC PERFORMANCE

The cardiorespiratory interactions in Figure 26.6 demonstrate that the effects of positive pressure are not limited to the lungs. The cardiac effects of positive pressure breathing are complex, and involve the preload and afterload forces for the right and left sides of the heart (30).

Preload

The term “preload” refers to a force that stretches a resting muscle to a new length. An increase in preload (resting muscle length) increases the force of muscle contraction (as explained by the sliding filament model of muscle contraction). The preload force for the intact heart is the volume in the ventricles at the end of diastole, and *the Frank-Starling law of the heart* states that ventricular end-diastolic volume (preload) is the principal force that governs the strength of ventricular contraction (31). Thus, factors that affect preload can have a profound effect on cardiac output.

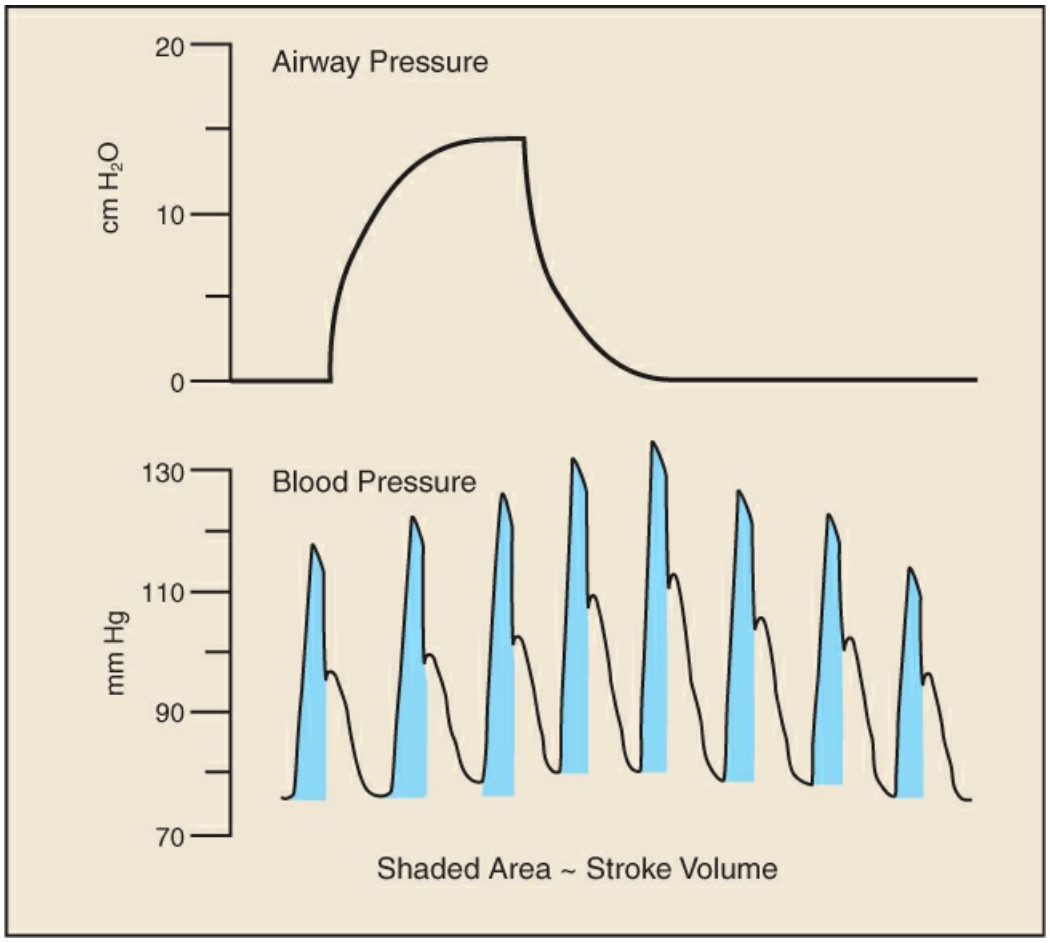

FIGURE 26.6 Changes in arterial pressure associated with a positive pressure breath. The increase in arterial pressure is a reflection of an increase in left ventricular stroke volume, as indicated by the shaded areas in the arterial pressure waveforms. See text for further explanation.

Positive Intrathoracic Pressure

Positive intrathoracic pressure can reduce ventricular preload (end-diastolic volume) in a number of ways. These are shown in Figure 26.7, and are summarized below.

. Positive intrathoracic pressure decreases the pressure gradient for venous inflow into the thorax, which decreases right ventricular filling.

. The positive intrathoracic pressures used during mechanical ventilation (noninvasive and invasive) often exceed the pressures in the pulmonary veins, and this compresses the veins and impedes left ventricular filling.

. Ventricular filling is a function of the end-diastolic *transmural* pressure (i.e., across the wall of the ventricles), so a positive pleural pressure will decrease this transmural pressure and thereby impede ventricular filling. This will have a greater effect on right ventricular filling, because the end-diastolic chamber pressure is lower in the right ventricle.

. High intrathoracic pressures will increase pulmonary vascular resistance, and this can impede right ventricular outflow. In patients with right ventricular systolic dysfunction, this can

increase right ventricular volume and push the interventricular septum toward the left ventricle, thereby reducing left ventricular filling.

Positive pressure breathing is thus a real threat to cardiac filling. This threat is magnified by hypovolemia, so avoiding hypovolemia is imperative during positive pressure ventilation (especially when high pressures are required for lung inflation).

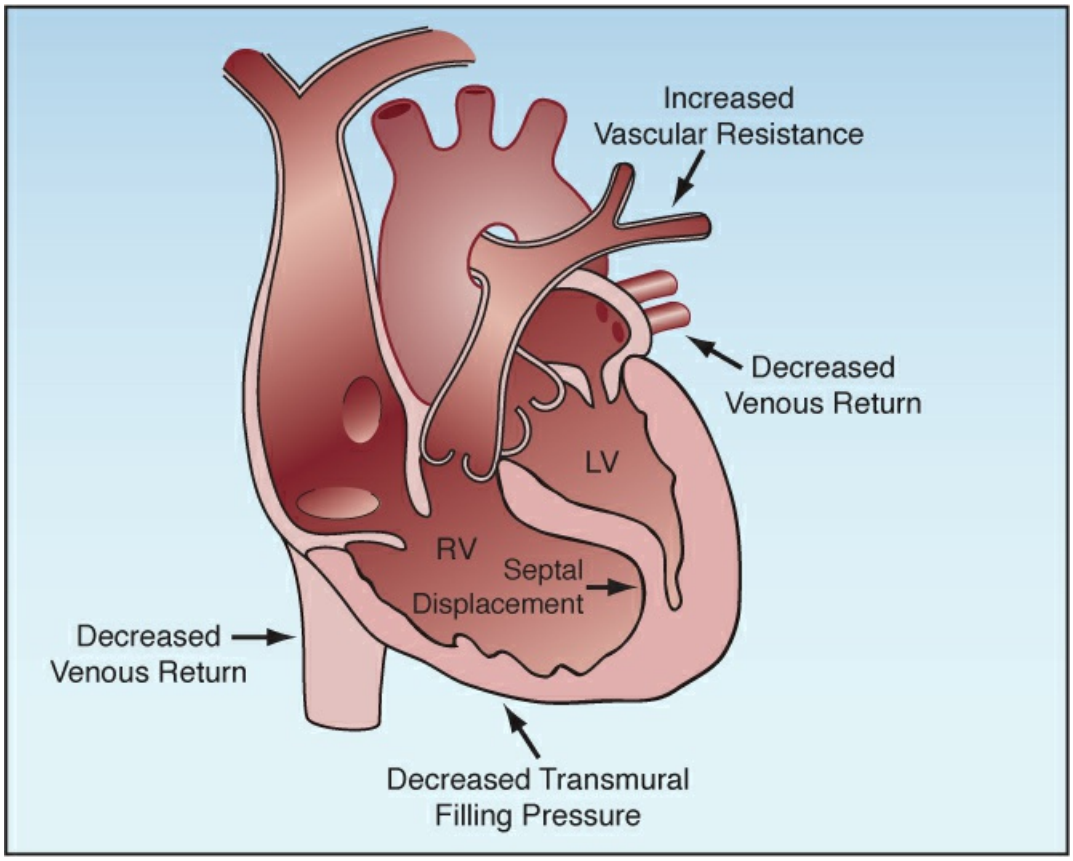

FIGURE 26.7 The different ways that positive intrathoracic pressure can decrease filling of the right and left ventricles.

Afterload

The term “afterload” refers to the force that must be overcome by muscle contraction. Unlike the preload force, which facilitates muscle contraction, the afterload force opposes muscle contraction. In the intact heart, *the afterload force is equivalent to the peak transmural wall pressure developed during systole*, which is the pressure needed to eject the stroke volume. This is a somewhat simplified view of afterload (which is more closely related to wall tension, and thus is dependent on wall thickness and chamber size), but it is adequate for describing the effects of positive pressure breathing.

Positive Intrathoracic Pressure

The determinants of left ventricular afterload are shown in Figure 26.8. There is a tendency to view afterload as a sole function of impedance and resistance in the systemic circulation, but afterload is a *transmural pressure*, and thus is also a function of the pleural pressure surrounding

the heart (in the absence of a pericardial effusion): i.e.,

$$\text{Afterload} = \text{Chamber Pressure} - \text{Pleural Pressure} \tag{26.1}$$

The negative intrathoracic (pleural) pressure that occurs during spontaneous breathing will increase left ventricular afterload (by opposing the inward movement of the ventricular wall during systole), and this explains why the systolic blood pressure normally decreases during a spontaneous inspiration. An exaggeration of the inspiratory decrease in systolic blood pressure (>10 mm Hg) is a condition known as *pulsus paradoxus* (which is a misnomer, since the condition is not paradoxical), and this condition can be produced by exaggerated inspiratory efforts (32), as occurs in acute asthma.

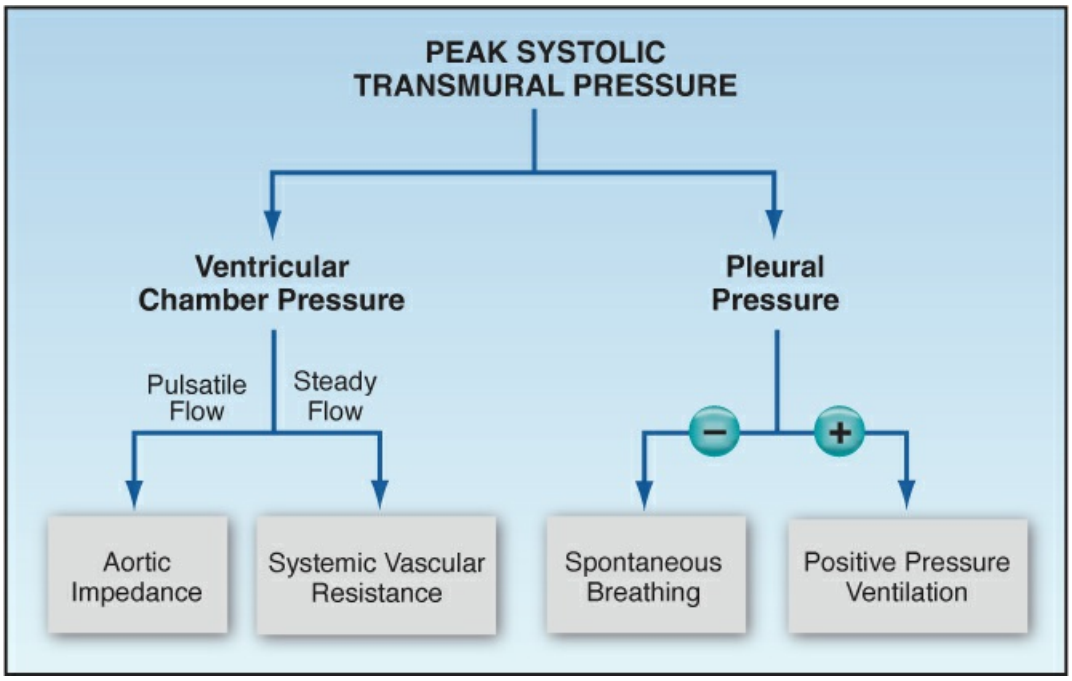

FIGURE 26.8 The determinants of left ventricular afterload. See text for explanation.

On the other hand, *positive intrathoracic pressure will decrease left ventricular afterload (by promoting the inward movement of the ventricle during systole)*, and this explains the inspiratory increase in systolic pressure in Figure 26.7. (This change is also known as *reversed pulsus paradoxus*.) Positive intrathoracic pressure thus assists the left ventricle in ejecting the stroke volume. This action is one of the proposed mechanisms for the ability of chest compressions to promote cardiac output (i.e., the thoracic pump model).

Cardiac Output

The overall effect of positive pressure ventilation on cardiac output will be determined by the balance between the preload and afterload effects of positive intrathoracic pressure, and this balance will be determined by three factors: the intravascular volume, the level of the intrathoracic pressure, and the presence or absence of cardiac dysfunction. The role of intravascular volume is mentioned previously, and the role of cardiac function is described next.

The Role of Cardiac Function

The following statements are based on the relationships between preload, afterload, and cardiac output in the normal and failing heart. These relationships are shown graphically in Figure 16.2.

. The normal heart operates on the steep portion of the preload curve and the flat portion of the afterload curve. In this situation, a decrease in preload has a greater influence on cardiac output than a decrease in afterload, so positive pressure ventilation is more likely to impair cardiac output by its actions to impede ventricular filling.

. In contrast, the failing heart operates on the flat portion of the preload curve and the steep portion of the afterload curve. In this situation, a decrease in afterload has a greater influence on cardiac output than a decrease in preload, so positive pressure ventilation is more likely to promote cardiac output by its actions to reduce left ventricular afterload. This would explain the benefit of CPAP and NIV in cardiogenic pulmonary edema, as described earlier.

These statements have two important implications. First, in patients with normal cardiac function, it is essential to maintain intravascular volume to support venous return during positive pressure ventilation. Second, in patients with left ventricular dysfunction, positive intrathoracic pressure can promote cardiac stroke output as long as it does not impede venous inflow to the right heart.

A FINAL WORD

Don’t Forget About Intubation

The popularity of noninvasive ventilation is based on the desire to avoid intubation, but there is a tendency to prolong noninvasive ventilation when there is no evidence of benefit, and this can be harmful. The following statements are relevant in this regard.

. Evidence of benefit should be evident after one hour of noninvasive ventilation. This evidence includes a decrease in $PaCO_2$ in hypercapnic respiratory failure, an increase in the PaO_2/FIO_2 ratio in hypoxemic respiratory failure, and alleviation of respiratory distress.

. Continued evidence of respiratory distress is particularly concerning, because it is often associated with increased spontaneous tidal volumes, and this can lead to *patient self-induced lung injury* (33) which is described in Chapter 24 (see Figure 24.4), and has been implicated in the failure of noninvasive ventilation (34).

. Delays to intubation creates unnecessary risk because emergent intubations in patients who are *in extremis* can be troublesome.

Although rarely viewed in a positive light, intubation and mechanical ventilation provide a greater level of ventilatory control, which may be necessary to slow or halt the progression of acute respiratory failure.

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Chapter 27

Conventional Mechanical Ventilation

Medicine is a science which has been more laboured than advanced.
For I find much iteration, but small addition.

Sir Francis Bacon (*a*)

The earliest ventilators (introduced in the late 1920s) were negative pressure chambers known as *iron lungs* that enclosed the patient from the neck to the ankles. These behemoths (early models weighed about a ton) were the sole means of ventilatory support until the polio epidemic in the 1950's, when the demand for assisted ventilation exceeded the supply of iron lungs. In Copenhagen, Denmark, tracheostomies were introduced, and medical students worked in 8 hour shifts as human ventilators, manually inflating the lungs of afflicted patients (1). In Boston, the local Emerson Company had a prototype device for positive pressure lung inflations, which was put to use at the Massachusetts General Hospital, and became an instant success.

Fast forward about 70 years, and there are estimated 174 different modes of ventilation (2). However, only one has shown evidence of improved clinical outcomes (3,4), and only because it limits the lung damage produced by positive pressure ventilation (see Chapter 24). What this means is that mechanical ventilation is much more complicated than it needs to be, and that "less is better" with this form of support.

This chapter describes the basic methods of positive pressure ventilation. Although far fewer than the bloated number of available methods, they will provide effective ventilatory support for most (if not all) of your patients.

THE VENTILATOR BREATH

There are two basic methods of positive-pressure lung inflation. These are summarized below, and are illustrated in Figure 27.1.

. *Volume-control ventilation*, where the desired inflation volume (tidal volume) is preselected. The gas is delivered at a constant flow rate, and there is a steady rise in volume and airway pressure until the target volume is reached. Exhalation is then passive.

. *Pressure-control ventilation*, where the desired inflation pressure is preselected. In this case,

the inspiratory flow rate has a decelerating pattern, with the peak flow rate in the initial phase of inspiration, and the flow rate then decreasing to zero by the end of inspiration. Because of this flow profile, the increments in lung volume and airway pressure are greater in the early phase of inspiration. The desired (peak) pressure is reached early, and a preselected inspiratory time then determines the end of inspiration. Exhalation occurs passively.

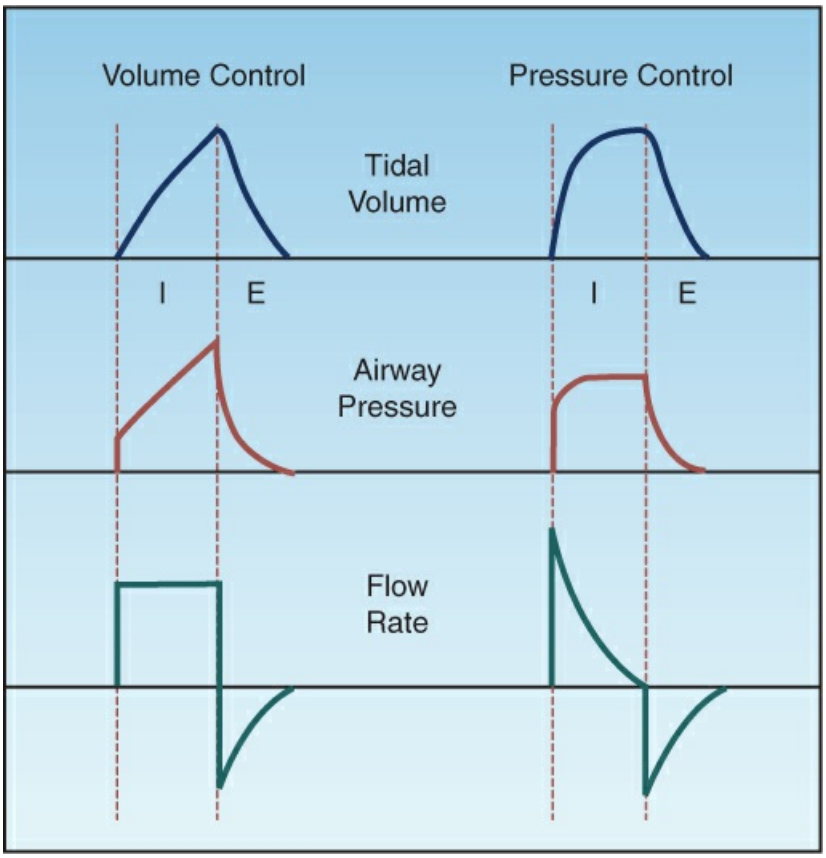

FIGURE 27.1 Changes in lung volume, airway pressure, and flow rate during a single ventilator breath using volume control and pressure control methods of lung inflation. I = inspiration, E = expiration. See text for further explanation.

All variables (i.e., volume, pressure, and flow) are recorded and displayed by the ventilator, but the measurements are made at the level of the endotracheal tube, and may not reflect conditions in the distal airspaces (the alveoli). In addition, the airway pressures are measured as *transthoracic* pressures (i.e., airway pressure relative to atmospheric pressure), and are influenced by both the lungs and the chest wall. The measurement of *transpulmonary* pressure (i.e., airway pressure relative to pleural pressure) eliminates the influence of the chest wall, but requires an esophageal balloon to measure the intrapleural pressure.

Volume Control

Volume-control ventilation (VCV) delivers a preselected tidal volume at a constant flow rate, and the peak airway pressure (Ppeak), is determined by the mechanical properties (resistance and elastance) of the lungs and chest wall. This can be expressed as follows:

$$\text{Ppeak} = \text{Pres} + \text{Pel} \tag{27.1}$$

where Pres is the pressure attributed to airflow resistance in the airways, and Pel is the pressure attributed to the elastic recoil force of the lungs and chest wall (elastance). (*Note:* Elastance is the resistance of an object to being deformed.)

The Plateau Pressure

The relative contributions of resistance and elastance to the peak airway pressure can be identified by briefly occluding the ventilator circuit at the end of lung inflation (5). This "inflation-hold" maneuver is illustrated in Figure 27.2. The peak pressure decreases initially during the inflation hold, and then reaches a constant *plateau pressure* until the occlusion is released and exhalation proceeds. Since there is no airflow during the inflation hold maneuver, the plateau pressure is equivalent to the pressure in the alveoli (Palv), and this is the pressure generated by the elastic recoil force of the lungs and chest wall (Pel): i.e.,

$$\text{Pplateau} = \text{Palv} = \text{Pel} \tag{27.2}$$

(*Note:* Positive end-expiratory pressure or PEEP is used commonly during mechanical ventilation, as described later, and this must be subtracted from the plateau pressure to obtain the actual alveolar pressure.) The difference between the peak and plateau pressures is then the pressure needed to overcome the resistance to airflow (Pres): i.e.,

$$(\text{Ppeak} - \text{Pplateau}) = \text{Pres} \tag{27.3}$$

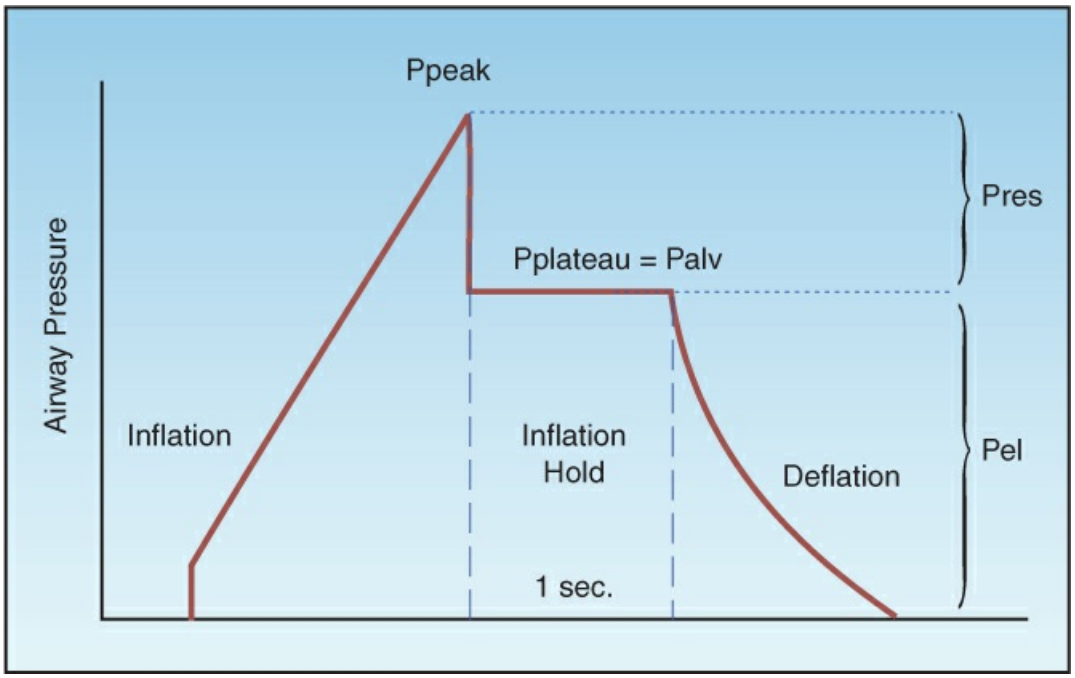

FIGURE 27.2 Airway pressure profile for a volume-controlled lung inflation with a brief end-inspiratory occlusion (inflation-hold). Ppeak is the peak airway pressure, Pplateau is the end-inspiratory occlusion pressure, Palv is the alveolar pressure, Pres is the pressure attributed to airway resistance, and Pel is the pressure attributed to the elastic recoil force of the lungs and chest wall. See text for explanation.

RISK OF ALVEOLAR INJURY: The peak airway pressure is higher with VCV than with pressure control ventilation (see Figure 27.1), and there is a misconception that this increases the risk of alveolar rupture. However, this risk is a function of the alveolar pressure; i.e., the plateau pressure. Clinical studies indicate that *the risk of alveolar rupture is negligible if the alveolar pressure (plateau pressure) is* $\leq$*30 cm* H_2O (2,4), and this is one of the major goals of *lung protective ventilation* (2), which is described later (see Table 27.1).

Advantages

The major advantage of VCV is the ability to maintain a constant tidal volume despite changes in the mechanical properties of the lungs. This is especially important for limiting the tidal volumes used during mechanical ventilation, which is the basis of lung protective ventilation.

Disadvantages

The constant inspiratory flow rate during VCV creates two potential disadvantages. First, the duration of inspiration is relatively short, and this can lead to uneven alveolar filling. Second, the maximum inspiratory flow is limited when flow is constant; as a result the inspiratory flow rate can be inadequate for patients with high ventilatory demands. A decelerating flow pattern is available for VCV, and has been shown to improve patient comfort (6).

Pressure Control

With pressure control ventilation (PCV), the desired inflation pressure is preselected, and a decelerating inspiratory flow rate provides high flows at the onset of the lung inflation, to attain the desired inflation pressure quickly. The inspiratory time is adjusted to allow enough time for the inspiratory flow rate to fall to zero at the end of inspiration. *Since there is no airflow at the end of the inspiration, the end-inspiratory airway pressure is equivalent to the alveolar pressure*.

Advantages

The major advantage of PCV is the increased patient acceptance and reduced risk of ventilatory asynchrony when compared to VCV (7). This advantage is attributed to the high initial flow rates and the longer duration of inspiration with PCV.

Disadvantages

The major disadvantage with PCV is the change in tidal volume that occurs with changes in airway resistance or lung elastance, since this can increase the risk of alveolar overdistension and ventilator-induced lung injury (see Chapter 24). However, this disadvantage is corrected with the adaptive mode of ventilation described next.

Pressure-Regulated, Volume Control

Pressure-regulated, volume control ventilation (PRVC) is an adaptive mode of ventilation that provides a constant tidal volume (like volume control) but limits the end-inspiratory airway pressures (like pressure control). PRVC operates like an intelligent form of volume control; i.e., the ventilator monitors lung compliance, and uses these measurements to select the lowest airway pressure needed to deliver the desired tidal volume (8). This has become a popular mode of mechanical ventilation, but patients with a high ventilatory drive may not receive the needed

inspiratory flow rate, leading to ventilator asynchrony (9).

End-Expiratory Pressure

The end-expiratory pressure is the minimum pressure in the alveoli during a ventilatory cycle. The different forms of end-expiratory pressure are illustrated in Figure 27.3.

ZEEP

During appropriate ventilation in the normal lung, there is no airflow at the end of expiration, and the pressure in the alveoli is equivalent to atmospheric pressure. Since atmospheric pressure is a zero reference point for breathing, this condition is called *zero end-expiratory pressure*, or ZEEP.

Applied PEEP

Positive end-expiratory pressure (PEEP) can be added through the ventilatory circuit (via a pressure-sensitive valve in the expiratory limb of the circuit) so that exhalation will cease when the airway pressure falls to the preselected PEEP level. Applied PEEP is used routinely during mechanical ventilation to prevent the collapse of small airways at the end of expiration, and to open collapsed alveoli (recruitment). The uses, advantages, and disadvantages of applied PEEP are described later in the chapter.

Occult PEEP

When there is continued airflow at the end of expiration, the lungs do not completely empty, and the alveolar pressure remains positive even though the proximal airway pressure falls to atmospheric (zero) pressure. This pressure is sometimes called intrinsic PEEP or auto-PEEP, but *occult PEEP* is also used because the PEEP *is not apparent in proximal airway pressure recordings* (10). Occult PEEP can be the result of dynamic hyperinflation in patients with asthma and COPD, as described in Chapter 23, or it can be the result of ventilator settings that predispose to end-expiratory airflow (e.g., high tidal volumes, decreased time for exhalation).

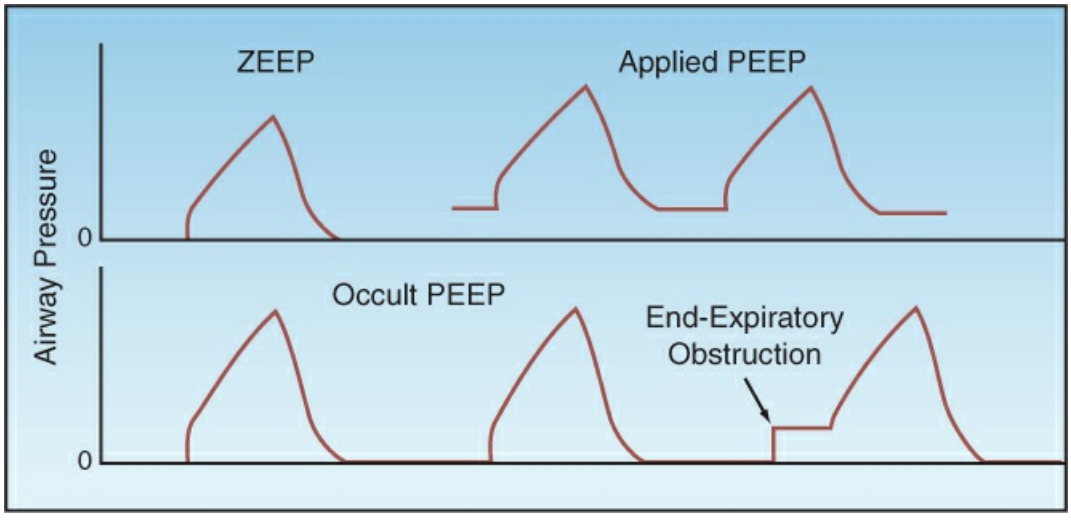

FIGURE 27.3 Different types of end-expiratory pressure. See text for explanation.

Occult PEEP can be detected on the flow tracing by noting the presence of airflow at the end of expiration, as illustrated in Figure 23.5. If occult PEEP is present, it can be quantified by occluding the expiratory circuit at the end of expiration. During an end-expiratory occlusion, alveolar pressure will equilibrate with proximal airway pressure, and the occult PEEP becomes apparent as a abrupt increase in airway pressure, as shown in Figure 27.3. This maneuver is successful *only in patients who have no respiratory efforts*. Occult PEEP is described in more detail in Chapter 28.

Mean Airway Pressure

The mean airway pressure is the average pressure in the airway during the ventilatory cycle, and is influenced by several variables, including the peak airway pressure, the contour of the pressure waveform, the PEEP level, the respiratory rate, and the inflation time relative to the total time of the ventilatory cycle (T_I /T_{tot}). The mean airway pressure that is displayed by ventilators is obtained by integrating the area under the airway pressure waveform.

The mean airway pressure is linked to the hemodynamic effects of positive pressure ventilation. (The intrapleural pressure is the important influence on cardiac function, but this pressure requires measurement with an intraesophageal balloon, and is not monitored routinely.) Typical values for mean airway pressure during positive pressure ventilation are 5–10 cm H_2O for normal lungs, 10–20 cm H_2O for airflow obstruction, and 20–30 cm H_2O for noncompliant (stiff) lungs (11).

Thoracic Compliance

Compliance (Δvolume/Δpressure) is the reciprocal of elastance, and is the traditional term used to express the elastic properties of structures with chambers (like the heart and lungs). Compliance expresses *distensibility*, or the tendency of a chamber to increase in volume when exposed to a given distending pressure. The compliance that is measured during mechanical ventilation is a *thoracic compliance*, and includes both the lungs and the chest wall.

Volume-Control Ventilation

During VCV, the static compliance of the thorax (Cstat) is expressed as the preselected tidal volume (VT) divided by the difference between the plateau pressure and the total PEEP level (applied plus occult PEEP):

$$Cstat = V_T/[Pplateau – PEEP(tot)] \quad (27.4)$$

This is a “static” compliance because the pressures involved are measured in the absence of airflow. In patients with normal lungs, Cstat is 50–80 mL/cm H_2O (12), and in patients with infiltrative lung diseases (e.g., pulmonary edema or acute respiratory distress syndrome), Cstat is typically <25 mL/cm H_2O (13).

Pressure-Control Ventilation

During PCV, Cstat is the exhaled tidal volume (exhaled V_T) divided by the difference between the end-inspiratory airway pressure (Paw) and the total PEEP level:

$$\text{Cstat} = \text{Exhaled } V_T/[\text{Paw(end-insp)} - \text{PEEP(tot)}] \quad (27.5)$$

Sources of Error

. During passive ventilation, the chest wall can account for 35% of the total thoracic compliance (14,15), and this contribution increases when the chest wall muscles contract. Therefore, to avoid errors in interpreting changes in thoracic compliance, the *compliance measurements should be performed in patients with minimal or no breathing efforts*.

. Thoracic compliance is volume-dependent; i.e., it decreases as lung volume increases. Absolute lung volumes cannot be measured during mechanical ventilation, so *compliance measurements should be performed at the same tidal volume*.

. The tidal volume used for the compliance measurement should be adjusted for the compliance of the ventilator tubing, which is typically 3 mL/cm H_2O (13). For example, if the preselected tidal volume during VCV is 500 mL and the peak airway pressure is 40 cm H_2O, then 3 × 40 = 120 mL of the delivered volume will be lost to expansion of the ventilator tubing, and the actual tidal volume reaching the patient will be 500 – 120 = 380 mL. When using exhaled tidal volumes during PCV, the airway pressure at end-inspiration should be used for the volume adjustments.

ASSIST-CONTROL VENTILATION

Assist-control ventilation (ACV) allows the patient to initiate the ventilator breath, but if this is not possible, ventilator breaths are delivered at a preselected rate (controlled or time-triggered ventilation). The ventilator breaths during ACV can be volume-cycled or pressure-cycled.

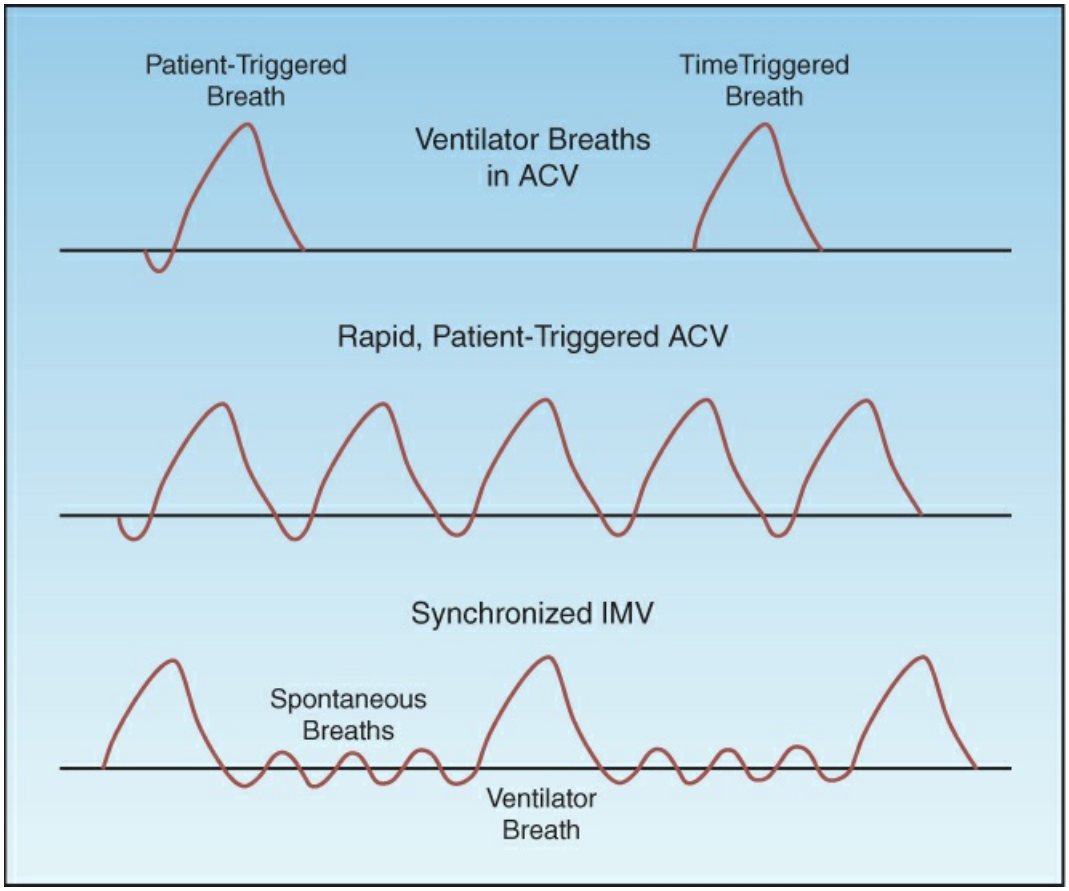

FIGURE 27.4 Airway pressure patterns in assist-control ventilation (ACV) and synchronized intermittent mandatory ventilation (SIMV). See text for further explanation.

Triggers

The ventilator breaths in ACV can be initiated (triggered) in two ways, as shown in the upper panel of Figure 27.4. The pressure waveform on the left is preceded by a negative pressure deflection, which represents a spontaneous inspiratory effort by the patient. This is a *patient-triggered* ventilator breath. The pressure waveform on the right is not preceded by a negative pressure deflection, indicating the absence of a spontaneous inspiratory effort. In this case, there is no interaction between the patient and the ventilator, and the ventilator breaths are delivered at a preselected rate. This is a *time-triggered* ventilator breath.

Patient-Related Triggers

There are two types of signals that allow patients to trigger a ventilator breath: negative pressure and inspiratory flow rate.

NEGATIVE PRESSURE: Patients can trigger a ventilator breath by generating a negative airway pressure of 2 to 3 cm H_2O, which opens a pressure-sensitive valve in the ventilator. Despite this low pressure requirement, about one-third of inspiratory efforts fail to trigger a ventilator breath when negative pressure is the trigger signal (16).

FLOW RATE: Flow triggering involves little or no change in pressures and volumes, and thus

involves less mechanical work than pressure triggering. For this reason, flow has replaced pressure as the standard trigger mechanism. The flow rate that is required to trigger a ventilator breath differs for each brand of ventilator, but rates of 1–10 L/min are usually required. Auto-triggering from system leaks (which create flow changes) is the major problem associated with flow triggering (17).

The Respiratory Cycle

A general rule of thumb during mechanical ventilation is to allow at least twice the amount of time for expiration as allowed for inspiration. This is equivalent to an inspiration:expiration time ratio (I:E ratio) of at least 1:2. The goal is to allow enough time for complete exhalation to prevent dynamic hyperinflation and intrinsic or occult PEEP (see Figure 23.5) If the duration of exhalation is too short, the I:E ratio can be increased by: (a) increasing the inspiratory flow rate, (b) reducing the tidal volume, or (c) decreasing the inspiratory time (for pressure control).

Rapid Breathing

When each breath is a patient-triggered ventilator breath, rapid breathing like that shown in Figure 27.4 can severely curtail the time for exhalation and increase the risk of dynamic hyperinflation and occult PEEP. When rapid breathing is the result of a condition other than discomfort or anxiety, attempts to reduce the respiratory rate with sedation or inspiratory flow adjustments are often unsuccessful. In this situation, the ventilator mode described next may be the answer.

INTERMITTENT MANDATORY VENTILATION

Difficulties with rapid breathing during ACV in neonates with respiratory distress syndrome, who typically have respiratory rates above 40 breaths/minute, led to the introduction of *intermittent mandatory ventilation* (IMV).

The Method

IMV is designed to allow spontaneous breathing between ventilator breaths. This is accomplished by placing a spontaneous breathing circuit in parallel with the ventilator circuit, with a unidirectional valve that opens the spontaneous breathing circuit when a ventilator breath is not being delivered. The ventilatory pattern in IMV is illustrated in the lower panel of Figure 27.4. Note that the ventilator breath is delivered in synchrony with the spontaneous breath, which is called *synchronized IMV* (SIMV).

The ventilator breaths during SIMV can be volume-cycled or pressure-cycled. The rate of ventilator breaths can be started at 10 breaths/min, and then adjusted as needed to achieve the desired minute ventilation (spontaneous plus assisted breaths).

Adverse Effects

The principal adverse effects of IMV are: (a) an increased work of breathing, and (b) a decrease in cardiac output, primarily in patients with left ventricular dysfunction. Both effects are the result of the spontaneous breathing period.

Work of Breathing

The heightened work of breathing during the spontaneous breathing period in IMV is attributed to resistance in the ventilator circuit. Spontaneous breathing with pressure support, which is described in Chapter 26 (see Figure 26.2), overcomes the added resistance of the ventilator circuit and reduces the work of breathing (18). As a result, pressure-support ventilation (at 10 cm H_2O) is now used routinely during the spontaneous breathing periods in IMV.

Cardiac Output

As described in Chapter 26, positive pressure ventilation reduces left ventricular afterload and can increase cardiac output (see Figure 26.6) (19). IMV has the opposite effect and increases left ventricular afterload (during the spontaneous breathing periods), which results in a decrease in cardiac output in patients with left ventricular dysfunction (20).

Summary

The major indication for IMV is rapid breathing with incomplete exhalation during assist-control ventilation. The spontaneous breathing periods during IMV promote alveolar emptying and reduce the risk of air trapping and intrinsic PEEP. IMV can increase the work of breathing and impair cardiac output in patients with left ventricular dysfunction; as a result, *IMV is not advised for patients with respiratory muscle weakness or left heart failure*.

POSITIVE END-EXPIRATORY PRESSURE

Ventilator-dependent patients usually have an increase in airway resistance (e.g., from COPD) or a decrease in lung compliance (e.g., from lung consolidation), and both of these conditions promote the collapse of small airways and alveoli at the end of expiration. This impairs gas exchange in the lungs and promotes hypoxemia. In addition, collapsed airspaces can reopen in the ensuing lung inflation, and the repetitive opening and closing of small airways can damage the airway epithelium by generating excessive shear forces (21). This type of injury is called *atelectrauma* (22), and it is one of the mechanisms for *ventilator-induced lung injury* (which is described in detail in Chapter 24).

To combat this tendency for alveolar collapse, positive end-expiratory pressure (PEEP) is used routinely during mechanical ventilation. The standard practice is to begin with a pressure of 5–8 cm H_2O, but the optimal level of PEEP may differ for each patient, as described next.

Best PEEP

Relatively small levels of PEEP (5–10 cm H_2O) can prevent the collapse of distal airspaces, while higher PEEP levels (10–20 cm H_2O) can open airspaces that are collapsed. This latter effect is known as *alveolar recruitment*, and it increases the available surface area in the lungs for gas exchange (23). However, higher levels of PEEP can also overdistend and rupture alveoli in normal lung regions. This is known as *volutrauma*, and is the principal form of ventilator-induced lung injury (23). The following are some ways to determine whether PEEP is promoting alveolar recruitment (favorable response) or promoting alveolar overdistension (unfavorable response).

Lung Compliance

When PEEP is promoting alveolar recruitment, the compliance (distensibility) of the lungs will increase, but when PEEP is overdistending alveoli, lung compliance will decrease. Therefore, monitoring the changes in thoracic compliance (as in Equations 27.4 and 27.5) in response to incremental levels of PEEP can identify whether PEEP is beneficial or harmful. This is demonstrated in Figure 27.5 (24). The upper curve in this figure shows that compliance initially increases in response to PEEP, but eventually begins to decrease. The transition point then identifies the "best PEEP" level.

Driving Pressure

At any given tidal volume, lung compliance is a function of the difference between the peak alveolar pressure and the PEEP level (as shown in Equations 27.4 and 27.5). This pressure difference is the "driving pressure" for alveolar distension, and the changes in this pressure can identify if PEEP is promoting alveolar recruitment or overdistension. This is demonstrated in the lower curve in Figure 27.5 (24). The driving pressure decreases with lower levels of PEEP (indicating that alveolar recruitment is the predominant response), but begins to increase at higher levels of PEEP (indicating that alveolar overdistension is a risk), and the transition point is then the "best PEEP" level.

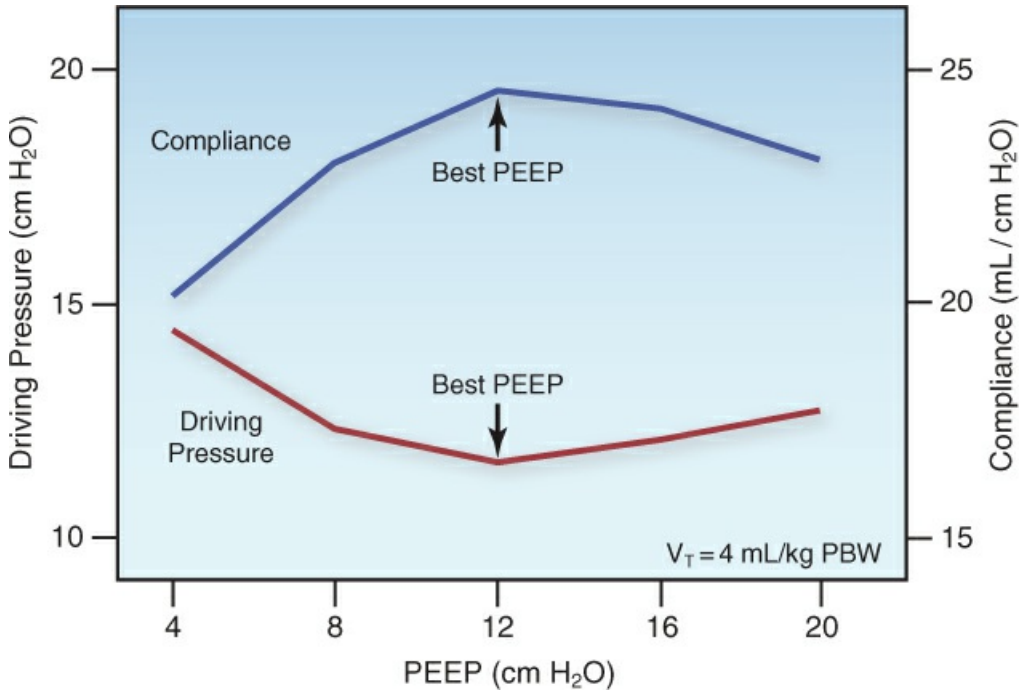

FIGURE 27.5 The effects of incremental levels of PEEP on thoracic compliance and driving pressure, which were measured at a constant tidal volume (V_T) of 4 mL/kg predicted body weight (PBW). The point of transition in each curve identifies the "best PEEP". Data from Reference 24. See text for further explanation.

PaO_2 /FIO_2 Ratio

The relationship between the arterial PO_2 and the fractional concentration of inspired oxygen, as expressed by the PaO_2/FIO_2 ratio, is a measure of the efficiency of gas exchange in the lungs.

When PEEP promotes alveolar recruitment, the PaO_2/FIO_2 ratio will increase, and when PEEP does not promote alveolar recruitment, the PaO_2/FIO_2 ratio will remain unchanged or will decrease. An example of a beneficial response in the PaO_2/FIO_2 ratio (indicating alveolar recruitment) is shown in Figure 27.6. However, an increase in the PaO_2/FIO_2 ratio is not synonymous with an increases in O_2 delivery to tissues, as explained next.

OXYGEN DELIVERY: The beneficial effects of PEEP on arterial oxygenation may not be accompanied by a similar benefit in oxygen delivery to tissues, because the rate of O_2 delivery in arterial blood (DO_2) is dependent on the cardiac output (CO) as well as the arterial O_2 content (CaO_2): i.e.,

$$DO_2 = CO \times CaO_2 \tag{27.6}$$

The effects of positive pressure ventilation that impair cardiac filling are described in Chapter 26 (see Figure 26.7), and PEEP magnifies these effects (25). This means that PEEP can decrease the cardiac output and negate the beneficial effects on arterial oxygenation. This is shown in Figure 27.6, where the progressive increase in PaO_2/FIO_2 ratio in response to incremental PEEP is accompanied by a progressive decrease in cardiac output (26). Thus, PEEP can promote alveolar recruitment and increase arterial oxygenation, but systemic O_2 delivery may not improve if PEEP also decreases the cardiac output.

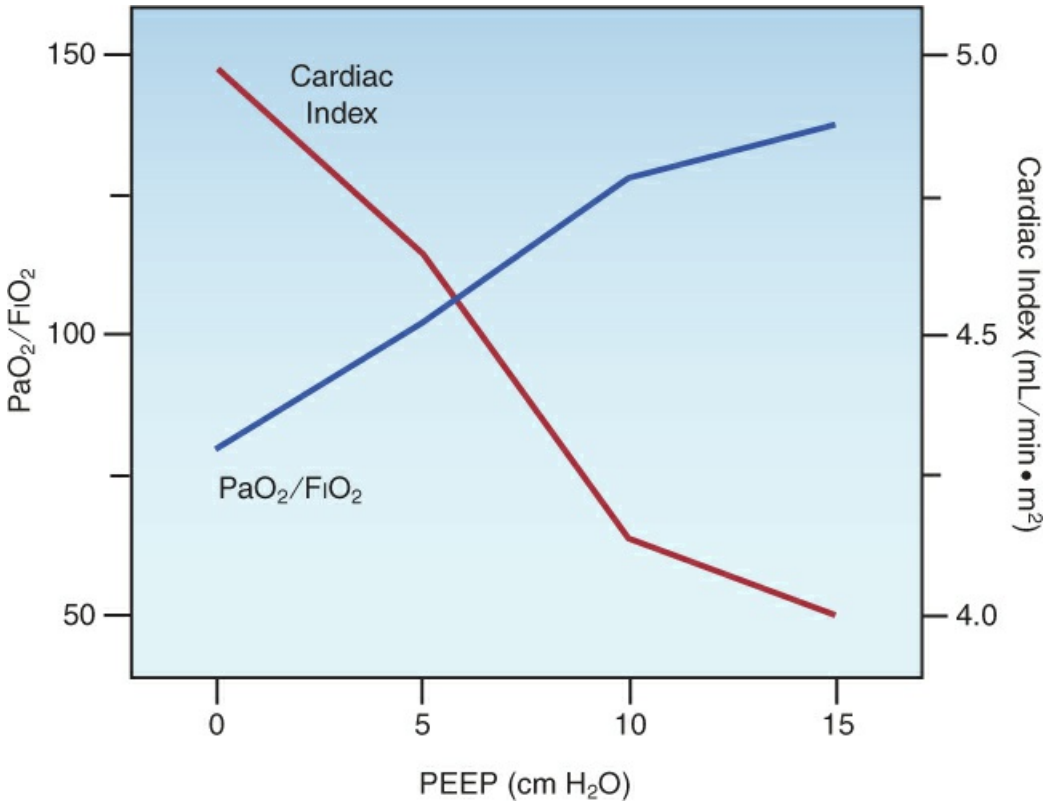

FIGURE 27.6 The opposing effects of positive end expiratory pressure (PEEP) on oxygenation (PaO_2/FIO_2) and cardiac index in patients with ARDS. Data from Reference 26.

The opposing effects of PEEP on arterial oxygenation and cardiac output emphasize the need to include a measure of systemic O_2 delivery in the determination of "best PEEP". Since cardiac output is not frequently monitored during mechanical ventilation, the central venous O_2 saturation can be used as a surrogate measure of changes in cardiac output and O_2 delivery, as explained in Chapter 9.

VENTILATOR SETTINGS

When mechanical ventilation is initiated, the respiratory therapist will ask you for the following parameters: (a) mode of ventilation, (b) tidal volume, (c) respiratory rate, (d) PEEP level, and (e) inspired O_2 concentration. The following is a list of suggestions for setting up mechanical ventilation.

Assist-Control Ventilation

. Select assist-control as the initial mode of ventilation.

. It may be necessary to switch to synchronized IMV in patients who are breathing too rapidly in the assist-control mode (see later).

Volume vs. Pressure Control

. Use volume control of some form (either standard volume control or pressure-regulated volume control) in order to use *lung protective ventilation*, where control of the tidal volume is a necessity.

. If lung protective ventilation is not improving gas exchange in patients with ARDS, consider switching to "airway pressure release ventilation" (see Figure 24.7).

Tidal Volume

The following recommendations are from the protocol for lung protective ventilation, which is summarized in Table 27.1.

. Select an initial tidal volume of 8 mL/kg using *predicted body weight*. (The formulas for predicted body weight are in Table 27.1.)

. Reduce the tidal volume to 6 mL/kg over the next 2 hours, if possible.

. Monitor the end-inspiratory alveolar pressure (i.e., the plateau pressure) and keep it ≤30 cm H_2O (to limit the risk of volutrauma).

TABLE 27.1 Protocol for Lung Protective Ventilation

First Stage	1. Calculate patient's predicted body weight (PBW). Males: PBW = 50 + [2.3 x (height in inches – 60)] Females: PBW = 45.5 + [2.3 x (height in inches – 60)]

	2. Set initial tidal volume (V_T) at 8 mL/kg PBW. 3. Add positive end-expiratory pressure (PEEP) of 5 cm H_2O. 4. Select the lowest FIO_2 that achieves an SpO_2 of 88–95%. 5. Reduce V_T by 1 mL/kg every 2 hrs until V_T = 6 mL/kg.
Second Stage	1. When V_T = 6 mL/kg, measure plateau pressure (Ppl). 2. If Ppl >30 cm H_2O decrease V_T in 1 mL/kg increments until Ppl <30 cm H_2O or V_T. = 4 mL/kg.
Third Stage	1. Monitor blood gases for respiratory acidosis. 2. If pH = 7.15–7.30, increase respiratory rate (RR) until pH >7.30 or RR = 35 bpm. 3. If pH <7.15, increase RR to 35 bpm. If pH is still <7.15, increase V_T in 1 mL/kg increments until pH >7.15.
Optimal Goals	V_T = 6 mL/kg, Ppl ≤30 cm H_2O, SpO_2 = 88–95%, pH = 7.30–7.45.

Adapted from the protocol developed by the ARDS Network, available at www.ardsnet.org.

Inspiratory Flow Rate

. Select an inspiratory flow rate of 60 L/min if the patient is breathing quietly or has no spontaneous respirations.

. Use higher inspiratory flow rates (e.g., ≥80 L/min) for patients with respiratory distress or a high minute ventilation (≥10 L/min).

I:E Ratio

. The I:E ratio should be ≥1:2.

. If the I:E ratio is <1:2, the options for increasing the I:E ratio include: (a) increasing the inspiratory flow rate, (b) decreasing the tidal volume, or (c) decreasing the respiratory rate, if possible.

Respiratory Rate

. If the patient has no spontaneous respirations, set the respiratory rate to achieve your estimate of the patient's minute ventilation just prior to intubation, but do not exceed 35 breaths/minute.

. If the patient is triggering each ventilator breath, set the machine rate just below the patient's spontaneous respiratory rate.

. After 30 minutes, check the arterial PCO_2, and adjust the respiratory rate, if necessary, to achieve the desired PCO_2.

. For patients who are breathing rapidly and have an acute respiratory alkalosis or evidence of occult PEEP, consider switching to synchronized IMV (SIMV) as the mode of ventilation.

PEEP

. Set the initial PEEP to 5–8 cm H_2O.

. Further increases in PEEP may be necessary for the following reasons:

a. To increase the PaO_2/FIO_2 ratio in cases where a toxic level of inhaled oxygen (>60%) is required to maintain adequate oxygenation (SaO_2 ≥90%).

b. To determine the "best PEEP" for that patient.

Occult PEEP

. Check the flow rate at the end of expiration: if the expiratory flow rate has not returned to zero at end-expiration, this is evidence of dynamic hyperinflation and occult PEEP (see Figure 23.5).

. If there is evidence of occult PEEP, attempt to prolong the time for expiration by increasing the I:E ratio using the maneuvers described previously.

. If increasing the I:E ratio is not possible or is not successful, then measure the level of occult PEEP with the end-inspiratory occlusion method, and add extrinsic PEEP at a level that is just below the occult PEEP. (The rationale for this maneuver is explained in Chapter 28.)

A FINAL WORD

A Loss of Focus

Since the advent of mechanical ventilation, an enormous amount of time and energy has been devoted to the development of newer methods of ventilation (174 of them at last count), with only one of these showing evidence of improved outcomes (and only because it involves a decrease in ventilatory support) (3). What has been lost in these endeavors is the simple fact that mechanical ventilation is a temporary support measure for acute respiratory failure, and is not a treatment modality for lung disease. Therefore, if we want to improve outcomes in ventilator-dependent patients, less attention should be given to the knobs on ventilators, and more attention should be directed at the diseases that create ventilator dependency.

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Chapter 28

The Ventilator-Dependent Patient

Eyes and ears are bad witnesses to men if they have souls that understand not their language.

Heraclitus
6th Century BC

This chapter describes the common practices and daily concerns involved in the care of ventilator-dependent patients. The focus is on artificial airways (endotracheal and tracheostomy tubes), the management of respiratory secretions, and mechanical complications of positive-pressure ventilation (i.e., barotrauma and occult PEEP). The infectious complications of mechanical ventilation are described in the next chapter.

ARTIFICIAL AIRWAYS

Positive pressure ventilation is delivered through a variety of plastic tubes that are passed into the trachea through the vocal cords (endotracheal tubes) or are inserted directly into the trachea (tracheostomy tubes). These tubes are equipped with an inflatable balloon at the distal end (called a cuff) that is used to seal the trachea and prevent positive-pressure inflation volumes from escaping out through the larynx.

Endotracheal Tubes

Endotracheal (ET) tubes vary in length from 25 to 35 cm, and are sized according to their internal diameter, which varies from 5 to 10 mm (e.g., a size 7 ET tube will have an internal diameter of 7 mm). The size of the airways is primarily related to body height, and the recommended size of ET tubes according to height is as follows: size 7 ET tube for height ≤5 feet, 2 inches (5’2”), size 7.5 for height 5’3” to 5’10”, and size 8 for height of 5’11’’ or taller (1). Despite these recommendations, there is no evidence that ET tube size affects clinical outcomes (2).

Proper Tube Position

Evaluation of ET tube position is mandatory after intubation, and the portable chest film in

Figure 28.1 shows the proper position of an ET tube. When the head is in a neutral position, *the tip of the ET tube should be 3 to 5 cm above the tracheal bifurcation or midway between the bifurcation and vocal cords*. (This bifurcation is often identified as the *carina*, which is a ridge of cartilage situated at the tracheal bifurcation.) If the bifurcation or carina is not visible, it can be located at the level of the T4–T5 interspace on a portable chest x-ray. Flexion or extension of the head and neck causes a 2 cm displacement of the tip of the endotracheal tube (3).

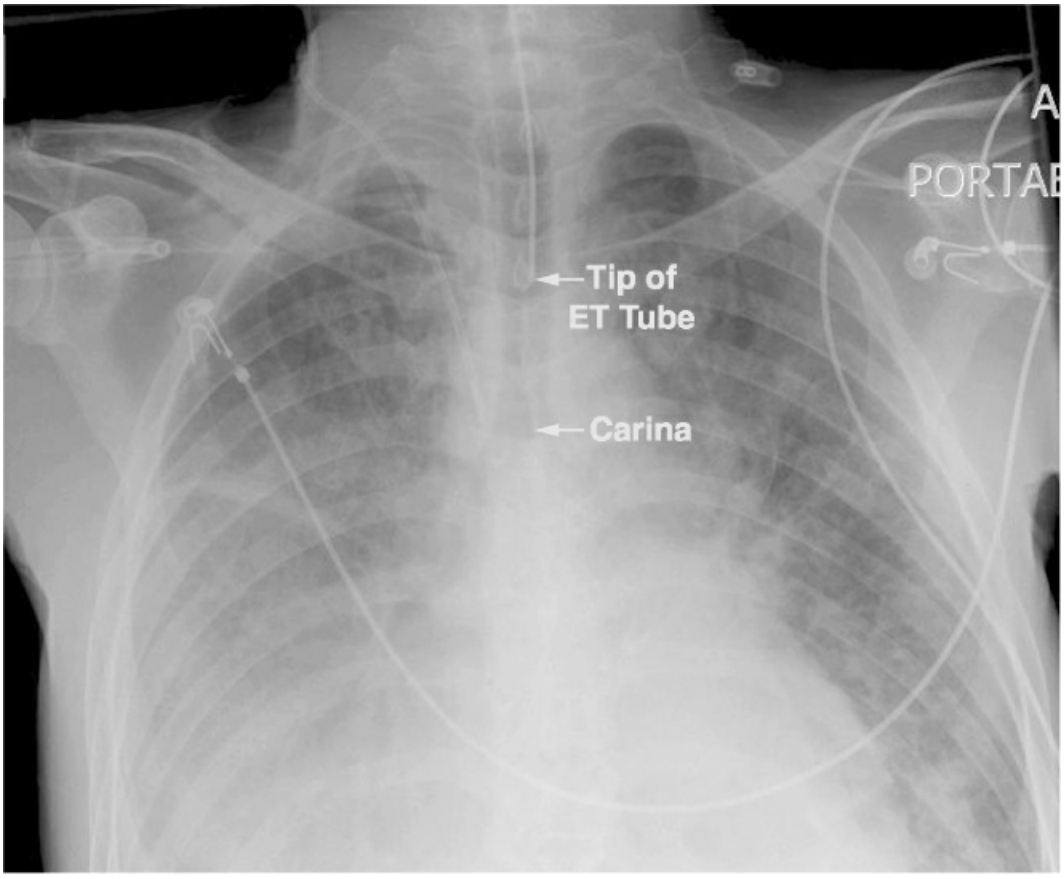

FIGURE 28.1 Portable chest x-ray showing proper position of an endotracheal tube, with the tip of the tube located midway between the thoracic inlet and the tracheal bifurcation (carina).

ESTIMATING LENGTH OF INSERTION: For endotracheal intubation, the proper length of ET tube insertion can be estimated by locating the manubriosternal joint, which forms a convex angle on the chest wall (known as the angle of Louis) that is in the same horizontal plane as the tracheal bifurcation. With the head fully extended, the distance between the upper incisors and the manubriosternal joint is the insertion distance that should place the tip of the ET tube in the appropriate position (4).

Migration of Tubes

ET tubes can migrate in either direction along the trachea (from manipulation of the tube during suctioning, turning, etc.), and when tubes move distally into the lungs, they often end up in the right mainstem bronchus (which runs a straight course down from the trachea). This is demonstrated in Figure 28.2 (5), which shows the tip of the ET tube in the right mainstem

bronchus, resulting in atelectasis of the non-ventilated left lung. The risk of ET tube migration can be reduced by keeping the tip of ET tube no further than 21 cm from the teeth in women and 23 cm from the teeth in men (6).

Laryngeal Damage

Laryngeal injury has been demonstrated in more than one-half of ICU patients that are intubated for longer than 12 hours (7), and is more common with difficult intubations, large ET tubes, and prolonged intubations. The spectrum of laryngeal damage includes posterior and subglottic ulceration, granulomas, and laryngeal edema. Long-term problems with voice and shortness of breath have been reported (7), and laryngeal edema can be problematic after extubation (described in Chapter 30).

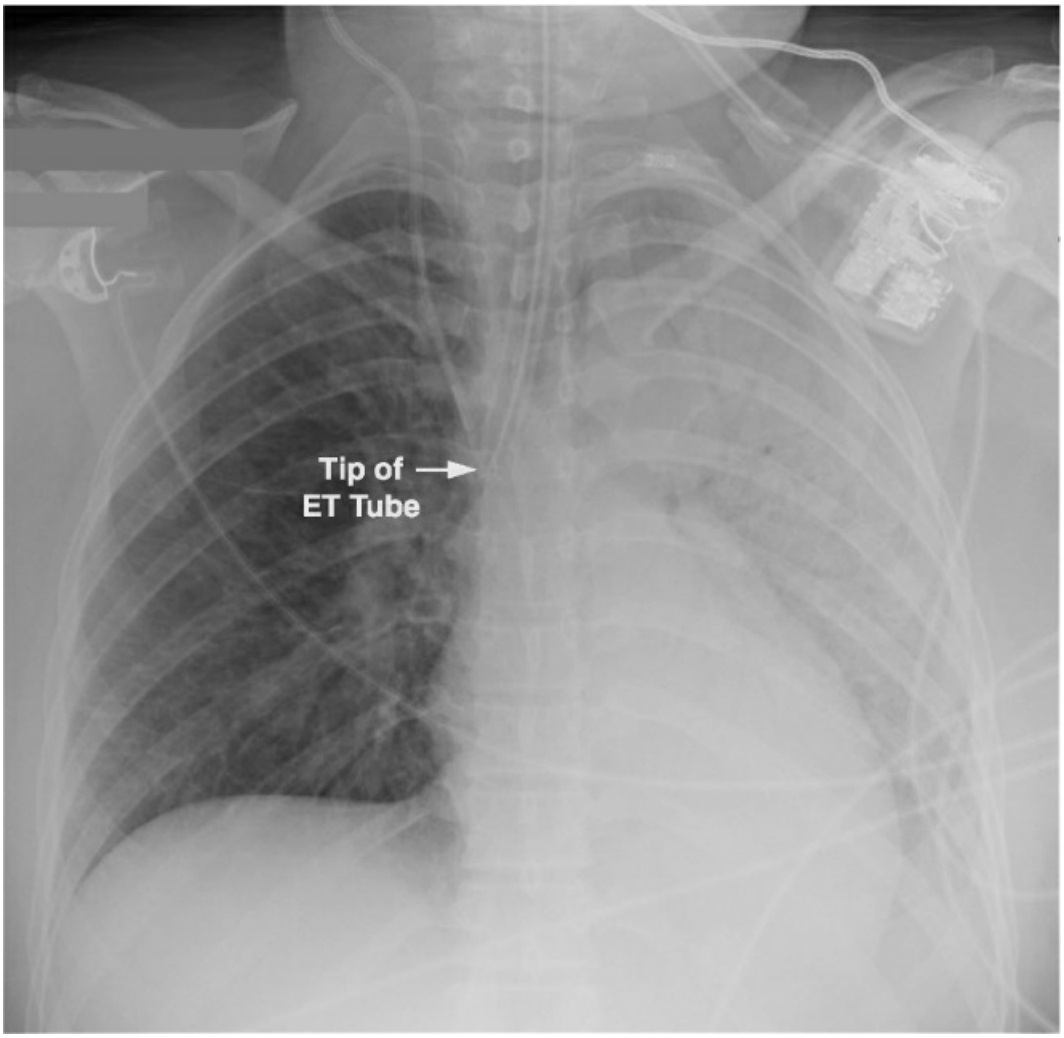

FIGURE 28.2 Portable chest x-ray showing intubation of the right mainstem bronchus and atelectasis of the non-ventilated left lung. Image from Reference 5.

Subglottic Drainage Tubes

The prominent role played by aspiration of mouth secretions in the pathogenesis of ventilator-associated pneumonia has led to the introduction of specially-designed endotracheal tubes

capable of draining mouth secretions that accumulate just above the inflated cuff. These tubes can reduce the incidence of ventilator-associated pneumonia (8), and they are described in more detail in the next chapter (see Figure 29.2).

Tracheostomy

Tracheostomy is preferred in patients who require prolonged mechanical ventilation (>2 weeks). The are several advantages with tracheostomy, including greater patient comfort, easier access to the airways for clearing secretions and bronchodilator administration, reduced resistance for breathing, and reduced risk of laryngeal injury.

Tracheostomy Timing

Several studies have compared early tracheostomy (within one week after intubation) with late tracheostomy (two weeks or later after intubation), and the bulk of the evidence shows that early tracheostomy can reduce sedative requirements and reduce the time on mechanical ventilation, but it does not reduce the incidence of ventilator-associated pneumonia, and does not reduce the mortality rate (9–11). The common practice is to *consider tracheostomy after one week of intubation if there is little chance of extubation in the following week*.

Techniques

The traditional method of performing a tracheotomy as an open surgical procedure has been replaced in popularity by *percutaneous dilatational tracheostomy*, where a guidewire is passed through a small needle puncture in the anterior wall of the trachea, and a tracheostomy tube is advanced over the wire and into the tracheal lumen. This technique, which is performed at the bedside, has several advantages over surgical tracheostomy (including less cost, avoiding general anesthesia, and fewer infections) (12), and is the preferred method of tracheostomy (13). However, the percutaneous technique has more technical difficulties than the surgical procedure (12), emphasizing the importance of a skilled and experienced operator.

The technique known as *cricothyroidotomy* is used only for emergency access to the airway. The trachea is entered through the cricothyroid membrane, just below the larynx, and there is high incidence of laryngeal injury and subglottic stenosis. Patients who survive following a cricothyroidotomy should have a regular tracheostomy (surgical or percutaneous) as soon as they are stable.

Complications

Combining surgical and percutaneous tracheostomy, the mortality rate is less than 1%, the incidence of major bleeding is <5%, and the infection rate is 2–10% (with the lower rates in the percutaneous tracheostomies) (12).

ACCIDENTAL DECANNULATION: One acute complication that deserves mention is accidental decannulation. If the tracheostomy tube is dislodged before the stoma tract is mature (which takes about one week) the tract closes quickly, and blind reinsertion of the tube can create false tracts. *If a tracheostomy tube is dislodged within a few days of insertion, the patient should be reintubated orally before attempting to reinsert the tracheostomy tube*.

TRACHEAL STENOSIS: The most feared complication of tracheostomy is tracheal stenosis, which is a late complication that appears in the first 6 months after the tracheostomy tube is removed. Most cases of tracheal stenosis occur at the site of the tracheal incision, and are the result of tracheal narrowing after the stoma closes. The incidence of tracheal stenosis ranges from zero to 15% in individual reports (14), but most cases are asymptomatic. The risk of tracheal stenosis is the same with surgical and percutaneous tracheostomies (15).

Cuff Management

Positive pressure ventilation requires a seal in the trachea that prevents gas from escaping out through the larynx during lung inflation, and this seal is created by inflatable balloons (called cuffs) that surround the distal portions of endotracheal and tracheostomy tubes. A tracheostomy tube with an inflated cuff is shown in Figure 28.3. The cuff is attached to a pilot balloon that has a one-way valve. A syringe is attached to the pilot balloon and air is injected into the cuff until there is no audible leak around the cuff. (The pilot balloon will inflate as the cuff inflates.)

The pressure in the cuff (measured with a pressure gauge attached to the pilot balloon) should not exceed 25 mm Hg (16). This pressure limit is based on the assumption that the capillary hydrostatic pressure in the wall of the trachea is 25 mm Hg, and thus external (cuff) pressures above 25 mm Hg can compress the underlying capillaries and produce ischemic injury in the tracheal mucosa. Modern cuffs have an elongated design that reduces the pressure needed for a tracheal seal.

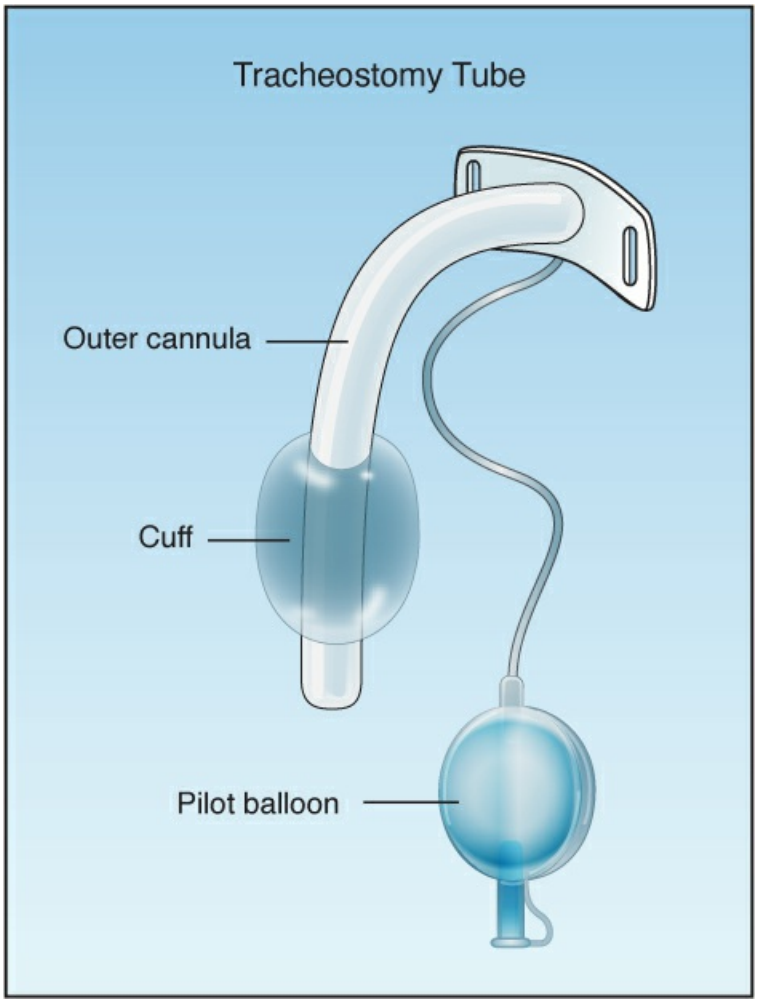

FIGURE 28.3 A tracheostomy tube with an inflated cuff.

Cuff Leaks

Cuff leaks are usually detected by audible sounds during lung inflation (created by gas flowing through the vocal cords). When a cuff leak becomes audible, the volume of the leak can be estimated as the difference between the desired tidal volume and the exhaled tidal volume measured by the ventilator. Cuff leaks are usually not caused by disruption of the cuff (17), but are instead the result of: (*a*) nonuniform contact between the cuff and the wall of the trachea, or (*b*) dysfunction of the valve on the pilot balloon.

TROUBLESHOOTING: If a cuff leak is apparent, the patient should be separated from the ventilator and the lungs should be manually inflated with an anesthesia bag. Then check the pilot balloon:

. If the pilot balloon is inflated, then the cuff is inflated, and the problem is likely to be a non-uniform seal with the wall of the trachea. In this situation, deflate the cuff, and reposition the tube, then re-inflate the cuff. (You can put more air into the cuff, but make sure the pressure does not exceed 25 cm H_2O). If this does not correct the leak, then replace the tube with a larger one.

. If the pilot ballon is deflated, then the likely problem is a faulty one-way valve on the pilot balloon, or a disrupted cuff. In this situation, attempt to re-inflate the cuff, and if the pilot balloon does not inflate, then replace the tube.

AIRWAY CARE

The clearance of respiratory secretions in intubated patients is often referred to as “pulmonary toilet”. However, because the lungs are not a toilet, the term “airway care” seems more appropriate.

Suctioning

Aspiration of airway secretions is a standard practice in the care of ventilator-dependent patients. However, this can have a number of unfavorable effects, including increases in heart rate, blood pressure, intracranial pressure, and occult PEEP (described later), and a decrease in arterial O_2 saturation (18). More importantly, biofilms containing pathogenic organisms are found on the inner surface of ET tubes and tracheostomy tubes (see Figure 28.4), and passing a suction catheter through the tubes can dislodge these biofilms and inoculate the lungs with pathogenic organisms (19). As a result of these risks, *clinical practice guidelines do not recommended routine suctioning of the airways* (18). Instead, suctioning should be performed only when there is evidence of respiratory secretions (see next).

Indications

The following are considered the best indicators for airway suctioning (18,20): (*a*) visible secretions in airway tubes or ventilator tubing, (*b*) auscultatory evidence of airway secretions, and (*c*) a sawtooth pattern on the ventilator flow waveform. Other indications could include x-ray evidence of segmental atelectasis and an abrupt decrease in arterial oxygenation, which could be the result of retained secretions.

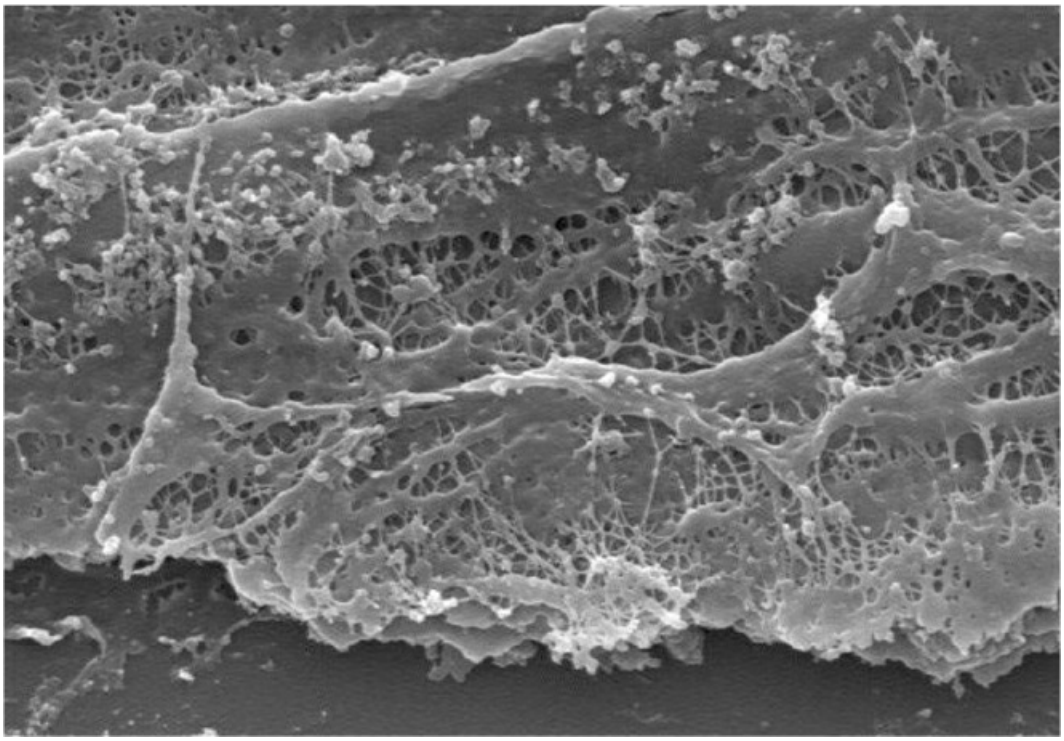

FIGURE 28.4 Electron micrograph showing a biofilm on the inner surface of an endotracheal tube. Image from Reference 19.

Saline Instillation

Once a standard practice, *the routine use of saline to facilitate the aspiration of secretions is NOT recommended* (18). There are two reasons for this: (*a*) saline will not reduce the viscosity of respiratory secretions (as described next), and (*b*) injection of saline can dislodge pathogenic organisms colonizing the inner surface of airway tubes. One study has shown that *injection of 5 mL of saline can dislodge up to 300,000 colonies of viable bacteria from the inner surface of endotracheal tubes* (21).

Viscosity of Respiratory Secretions

The respiratory secretions create a blanket that covers the mucosal surface of the airways. This blanket has a hydrophilic (water soluble) layer that faces inward to keep the mucosal surface moist, and a hydrophobic (water insoluble) layer that faces outward to trap particles and debris in the airways. This trapping is achieved by a meshwork of mucoprotein strands that are held together by disulfide bridges, and the combination of the mucoprotein meshwork and the trapped debris determines the viscoelastic behavior of the secretions. Thus, the layer that contributes to the viscosity of respiratory secretions is not water soluble, and hence *saline will not reduce the viscosity of respiratory secretions*. Adding saline to viscous respiratory secretions is like pouring water over grease.

Mucolytic Therapy

When respiratory secretions are thick and tenacious, a mucolytic agent like *N-Acetylcysteine* can help to clear the airways. N-acetylcysteine (NAC) is a sulfhydryl-containing tripeptide that is

better known as the antidote for acetaminophen overdose, but it is also a mucolytic agent that acts by disrupting the disulfide bridges between mucoprotein strands in respiratory secretions (22). The drug is available in a liquid preparation (10 or 20% solution) that can be given as an aerosol spray, or injected directly into the airways (Table 28.1). Aerosolized NAC is irritating and can provoke coughing and bronchospasm (especially in asthmatics), and direct instillation of NAC into the airway should be preferred for clearing secretions in ventilator-dependent patients.

TABLE 28.1 Mucolytic Therapy with N-Acetylcysteine (NAC)

Method	Regimen
Aerosol Therapy	• Use 10% NAC solution. • Mix 2.5 mL NAC with 2.5 mL saline and place mixture (5 mL) in a small volume nebulizer for aerosol delivery. Can repeat every 8 hrs. • Warning: Aerosol NAC can provoke bronchospasm, and is not recommended in asthmatics.
Tracheal Injection	• Use 20% NAC solution. • Mix 1 mL NAC with 1 mL saline and inject (2 mL) into the trachea. Can repeat every 8 hrs. • Warning: Prolonged use (>48 hrs) can promote bronchorrhea.

PULMONARY BAROTRAUMA

As described in Chapter 24, one of the principal mechanisms of ventilator-induced lung injury is overdistension of alveoli in normal lung regions (23), which ruptures the alveolar-capillary interface (see Figure 24.6). This is known as *volutrauma*, and it produces an inflammatory infiltration in the lung that is very similar to the acute respiratory distress syndrome (ARDS). Another consequence of alveolar rupture is the escape of gas from the distal airspaces, but this is called *pulmonary barotrauma*. If you are confused about the terms volutrauma and barotrauma, consider that *volutrauma is an expression of the strain (i.e., degree of deformation) on alveoli, while barotrauma is an expression of stress (i.e., the forces that produce deformation) imposed on alveoli, which is the transpulmonary pressure* (24).

Clinical Presentation

Escape of gas from the alveoli can produce a variety of clinical manifestations. The alveolar gas can dissect along tissue planes and produce *pulmonary interstitial emphysema*, and can move into the mediastinum and produce *pneumomediastinum*. Mediastinal gas can move into the neck to produce *subcutaneous emphysema*, or can pass below the diaphragm to produce *pneumoperitoneum*. Finally, if the rupture involves the visceral pleura, gas will collect in the pleural space and produce a *pneumothorax*. Each of these entities can occur alone or in combination with the others.

Pneumothorax

The incidence of pneumothorax is 3–10% in ventilator-dependent patients who receive limited-volume “lung protective ventilation” (25), and it has been reported in 35% of patients with COVID-19 pneumonia (mode of ventilation unknown) (26). In addition to barotrauma,

iatrogenic pneumothoraces can be the result of procedures (i.e., insertion of central venous catheters, thoracentesis, and bronchoscopy).

Clinical Presentation

Pneumothoraces from procedures can be small and clinically silent, while those caused by barotrauma are usually larger and can cause hypoxemia and even hypotension (see later). *The most specific clinical finding is subcutaneous emphysema*, which appears initially in the neck and upper thorax. The absence of breath sounds is an unreliable finding in ventilator-dependent patients because sounds transmitted from the tracheal tubes and ventilator tubing can be mistaken for airway sounds.

Radiographic Detection

The radiographic *detection of pleural air can be difficult in the supine position, because pleural air does not collect at the lung apex when patients are supine* (27). This is illustrated in Figure 28.5. In this case of a traumatic pneumothorax, the chest x-ray is unrevealing, but the CT scan reveals an anterior pneumothorax on the left. Pleural air will collect in the most superior region of the hemithorax, which in the supine position, is the region just anterior to both lung bases. Therefore, *basilar and subpulmonic collections of air are characteristic of pneumothorax in the supine position* (27).

Ultrasound Detection

Ultrasound of the lungs has consistently proven to be more sensitive than chest radiography for the detection of pneumothorax (28), but the yield is highly dependent on the skill and experience of the operator.

METHOD: The linear ultrasound probe is placed on the anterior chest and perpendicular to the 3rd or 4th intercostal space along the midclavicular line. The goal is to identify the pleural line (see Figure 28.6), a bright, hyperechoic line that represents the apposition of the parietal and visceral pleura. Normally, the visceral pleura moves along the parietal pleura as the lung inflates and deflates, and this sliding movement creates a shimmering effect on the ultrasound image. When air is present in the pleural space, the two pleural surfaces separate, and the sliding movement of the pleural line is lost. The absence of “lung sliding” is therefore suggestive (but not pathognomonic) of pneumothorax (29). (However, the presence of lung sliding rules out the diagnosis of pneumothorax.)

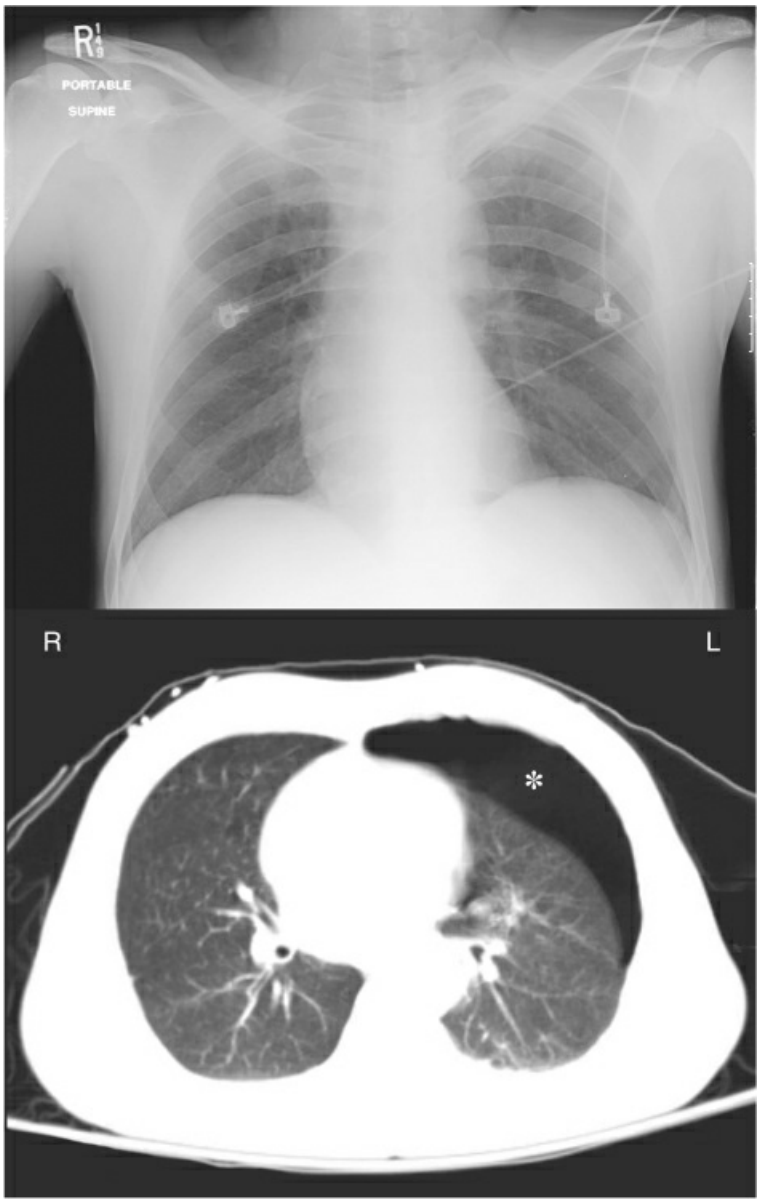

FIGURE 28.5 A portable chest x-ray and CT image of the thorax in a young male with blunt trauma to the chest. An anterior pneumothorax is evident on the CT image (indicated by the asterisk) but is not apparent on the portable chest x-ray.

When lung sliding is absent, the ultrasound probe should be moved laterally and inferiorly in increments, to reach the point where the two pleural surfaces meet again (at the edge of the pneumothorax), which is indicated by the return of lung sliding. This is known as the “lung point”, and it is pathognomonic of pneumothorax (29).

Tension Pneumothorax

Pleural air can accumulate rapidly when a pneumothorax is the result of positive pressure ventilation, and this accumulation can eventually produce a life-threatening *tension pneumothorax* where the increase in intrathoracic pressure collapses the ipsilateral lung, and causes a progressive decrease in cardiac output that culminates in “obstructive shock”, and

cardiac arrest from pulseless electrical activity. This condition should be considered in any ventilator-dependent patient who develops unexplained hypoxemia or hypotension. It is easily recognized on a portable chest x-ray, as shown in Figure 28.7 (30). Note the absence of lung markings in the left hemothorax (indicating complete collapse of the left lung), and the mediastinal shift to the right (indicating a marked increase in pressure in the left hemithorax. The left hemidiaphragm is also depressed, which is another sign of increased intrapleural pressure.

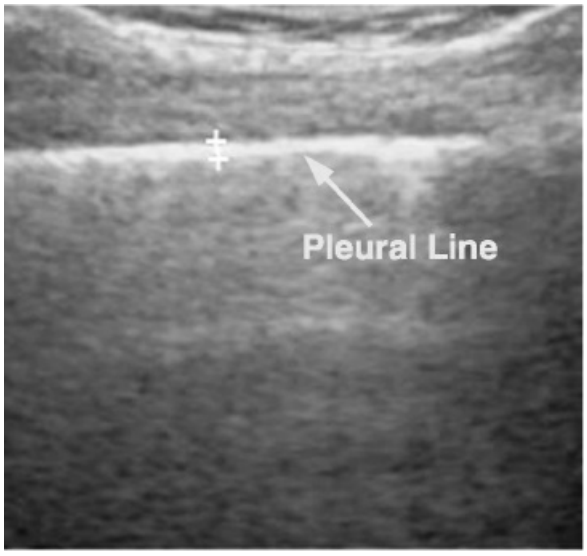

FIGURE 28.6 Ultrasound image showing the hyperechoic pleural line, which represents the apposition of the visceral and parietal pleura. A sliding movement in the pleural line with respirations occurs normally, and the absence of "lung sliding is suggestive of a pneumothorax. See text for further explanation.

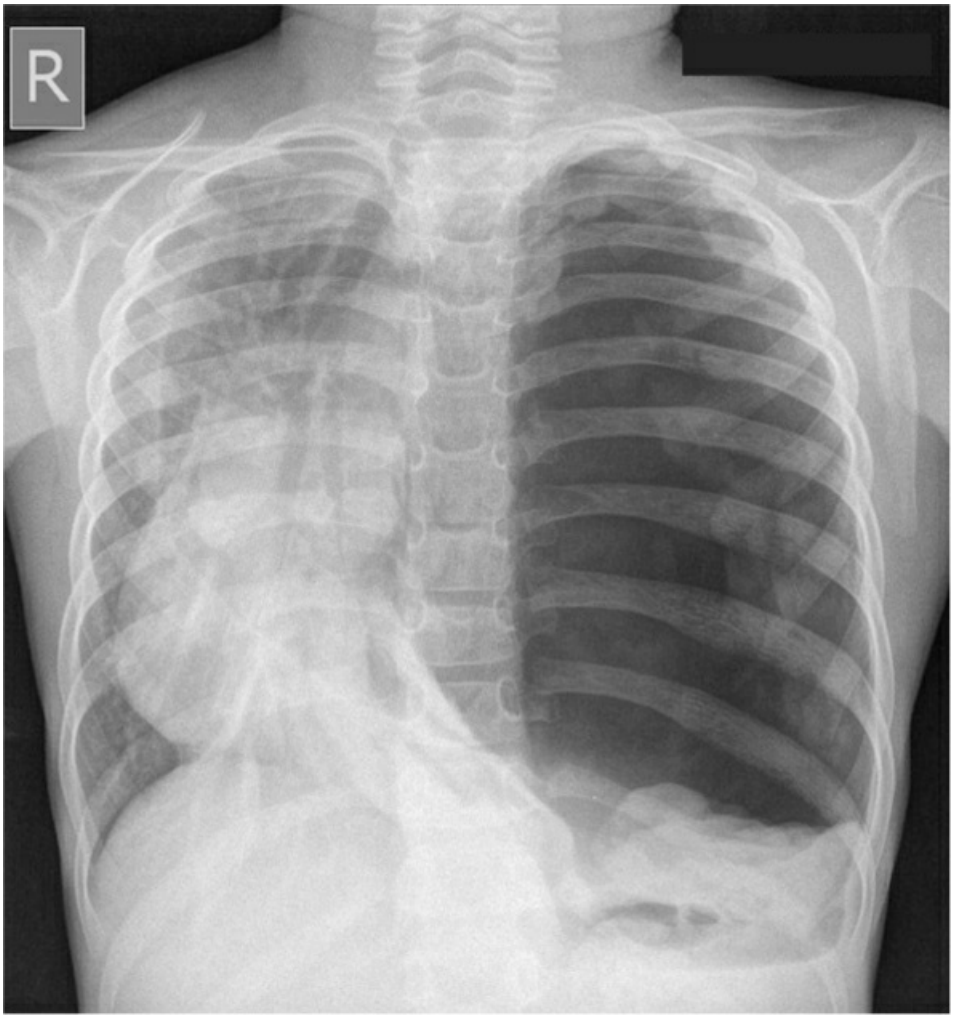

FIGURE 28.7 Tension pneumothorax. Note the absence of lung markings in the left hemithorax, with depression of the left hemidiaphragm and contralateral shift of the mediastinum. X-ray from Reference 30.

DECOMPRESSION: Tension pneumothorax is a medical emergency, and requires immediate decompression. The recommended procedure is insertion of a 14-gauge, 8 cm (3.25 inch) angiocatheter in the fifth intercostal space just anterior to the midaxillary line (31,32). (The failure rate is higher when shorter catheters are used, and when the catheters are inserted in the second interspace at the midclavicular line).

Needle decompression is not always successful, either because the needle does not reach the pleural space, or because the catheters kink or are dislodged. If this is the case, then "finger decompression" is recommended (i.e., placing a finger in the pleural space) (31). Following decompression, a small-bore chest tube (8.5–14 French) should be inserted.

Pleural Evacuation

Evacuation of pleural air is accomplished by inserting a chest tube through the fourth or fifth intercostal space along the mid axillary line. The tube should be advanced in an anterior and superior direction to evacuate air (and is directed inferiorly to evacuate fluid). Pleural evacuation

is achieved with a three-chamber system, which is depicted in Figure 28.8.

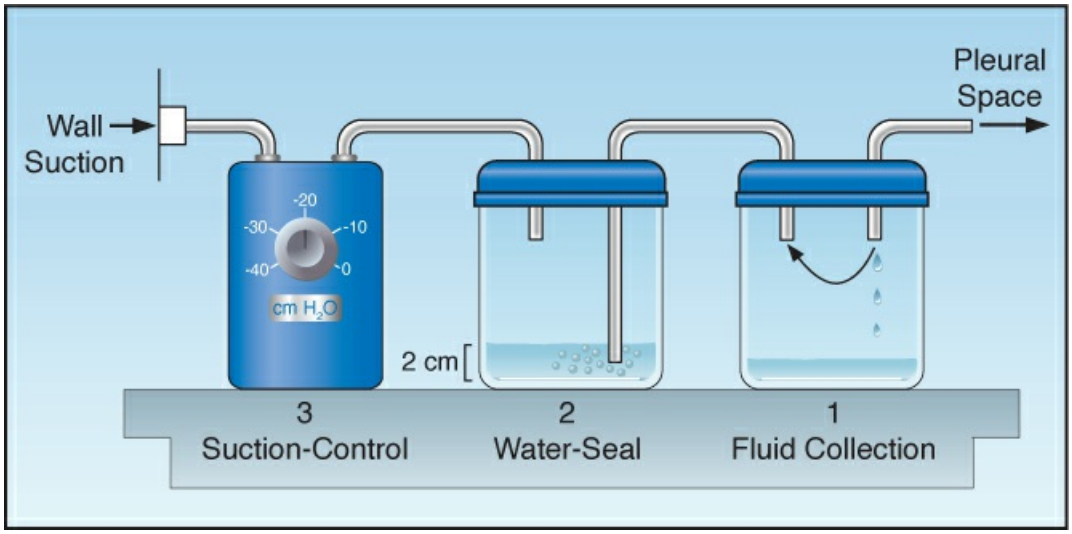

FIGURE 28.8 A three-compartment pleural drainage system for evacuating air and fluid from the pleural space.

Fluid Collection

The first chamber in the system collects fluid from the pleural space and allows air to pass through to the next chamber. Because the inlet of this chamber is not in direct contact with the fluid, the accumulating fluid does not exert a back pressure on the pleural space.

Water Seal Chamber

The second chamber creates a one way valve for the pleural space using a column of water (usually 2 cm in height) to produce a slightly positive pleural pressure (2 cm H_2O) that prevents atmospheric air from entering the pleural space. The water thus "seals" the pleural space from the surrounding atmosphere, hence this is called the "water seal chamber".

BUBBLING: Air that is evacuated from the pleural space will pass through the water and create bubbles. Thus, *the presence of bubbles in the water seal chamber is evidence of an air leak through a bronchopleural fistula (a hole in the lungs).*

Suction Control

The final component of the system is an adjustable valve that is connected to wall suction and controls the level of negative pressure used for pleural drainage. This pressure is usually set at –20 cm H_2O.

Why Suction?

The practice of using suction to evacuate pleural air is often unnecessary, and can be counterproductive. Suction may help to reinflate the lungs when the pleural air is evacuated, but thereafter the negative pressure in the pleural space will increase the transpulmonary pressure (the pressure difference between alveoli and the pleural space), and this will promote the flow of air through a bronchopleural fistula. Thus *applying suction to the pleural space will promote air*

leaks from the lungs and prevent the closure of bronchopleural fistulas. If there is a persistent air leak when suction is being applied to the pleural space, the suction should be turned off. Air leaks from the lungs will continue to be evacuated when the pleural pressure becomes more positive than the water seal pressure.

OCCULT (INTRINSIC) PEEP

Occult PEEP (also called intrinsic PEEP and auto-PEEP) is the result of incomplete emptying of the lungs. It is common in patients with severe airflow obstruction (e.g., it is responsible for the hyperinflation in acute asthma), and is exacerbated by rapid breathing and high tidal volumes (33). In ventilator-dependent patients, occult PEEP is considered universal in those with asthma and COPD (34,35), and low levels (≤3 cm H_2O) are also common in patients with ARDS (36).

Adverse Effects

Occult PEEP has several adverse effects, which are summarized below (33).

. Occult PEEP increases mean intrathoracic pressure, which can impair venous return and decrease cardiac output.

. The hyperinflation associated with occult PEEP increases the work of breathing because greater negative pressures are required to draw the tidal volume into the lungs. (To appreciate this effect, take a deep breath, and then try breathing from there.)

. Occult PEEP increases end-inspiratory alveolar volume and pressure, which increases the risk of volutrauma and barotrauma.

. Occult PEEP can be transmitted into the superior vena cava and create a spurious increase in central venous pressure measurements.

Monitoring Occult PEEP

As indicated by its name, occult PEEP is not evident in the airway pressures monitored during mechanical ventilation. It is easy to detect but difficult to quantify. Evidence of occult PEEP is provided by the expiratory flow waveform, which shows the presence of airflow at the end of expiration (see Figure 23.5). Determining the level of occult PEEP requires an end-expiratory occlusion maneuver.

End-Expiratory Occlusion

Occlusion of the expiratory circuit at the end of expiration will reveal occult PEEP, because in the absence of airflow, the pressure in the proximal airways will be equivalent to end-expiratory alveolar pressure. This is demonstrated in Figure 28.9. Accuracy requires that the occlusion occur at the very end of expiration, and this cannot be timed properly if patients are breathing spontaneously. Therefore, *the end-expiratory occlusion method is reliable only in patients who are not breathing spontaneously*.

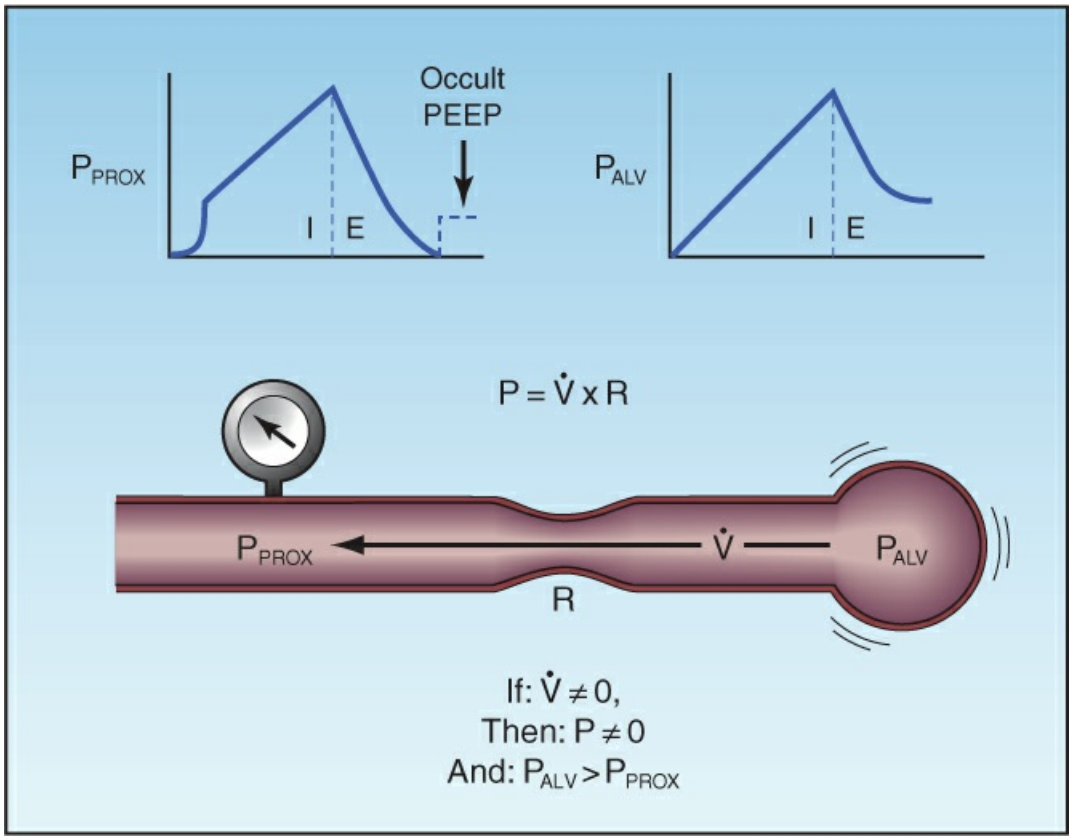

FIGURE 28.9 The features of occult PEEP. The presence of airflow (V) at end expiration indicates a pressure drop from the alveolus (PALV) to the proximal airways (PPROX). As shown at the top of the figure, the proximal airway pressure returns to zero at end expiration while the alveolar pressure remains positive; hence the term *occult* PEEP. The upper left panel illustrates the end expiratory occlusion method for measuring the level of occult PEEP.

Management

The maneuvers used to prevent or reduce hyperinflation and occult PEEP are all directed at promoting alveolar emptying during expiration. These maneuvers include reducing the tidal volume, increasing the inspiratory flow rate, reducing the inspiratory time (in pressure control ventilation), and reducing the respiratory rate, if possible. Some of these maneuvers will reduce the minute ventilation, which may not be desirable.

Applied PEEP

The addition of external PEEP can reduce hyperinflation (and occult PEEP) by holding the small airways open at end-expiration. The level of applied PEEP must be enough to counterbalance the pressure causing small airways collapse, but should not exceed the level of occult PEEP (so that it does not impair expiratory flow) (37). To accomplish this, the level of applied PEEP should be just below the level of occult PEEP. Since occult PEEP is difficult to quantify in spontaneously breathing patients, an alternative method is to monitor the level of end-expiratory airflow in response to applied PEEP; i.e., if the applied PEEP reduces or eliminates end-expiratory flow, then it is reducing the level of occult PEEP. However, the end result is still PEEP (applied PEEP instead of occult PEEP), but the applied PEEP will help to reduce the risk of atelectrauma from repetitive opening and closing of small airways at the end of expiration. (*Note:* The effect of

applied PEEP on occult PEEP is included for completeness, but attempting to reduce occult PEEP with applied PEEP is probably not worth the trouble.)

A FINAL WORD

The patient's clinical course in the first few days of mechanical ventilation will give you an indication of what is coming. If the patient is not improving after the first week, proceed to tracheostomy (for patient comfort and improved clearance of secretions). Most of the day-to-day management of the ventilator-dependent patient involves vigilance for adverse events (i.e., "putting out fires"). You will learn that, in many cases, you are not the one controlling the course of the patient's illness.

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Occult PEEP

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Chapter 29

Ventilator-Associated Pneumonia

Everything hinges on the matter of evidence.

Carl Sagan

Pneumonias that develop during mechanical ventilation can be characterized by one word: *problematic*. The problems include the nonspecific clinical presentation of ventilator-associated pneumonia, the uncertainties in identifying the culprit organism, and the difficulties created by the emergence of multidrug resistant organisms in this condition.

This chapter addresses the multiple problems encountered in the approach to ventilator-associated pneumonia, and includes recommendations from the most recent clinical practice guidelines on the subject (1,2).

GENERAL INFORMATION

The following statements include some basic information about ventilator-associated pneumonia (VAP).

. ICU-acquired pneumonias are divided into ventilator-associated pneumonia (VAP), with onset ≥48 hours after intubation, and hospital-acquired pneumonia (HAP), with onset ≥48 hours after ICU admission in nonintubated patients. VAP is further classified as early onset (2–4 days after intubation) or late-onset (≥5 days after intubation).

. VAP accounts for 80% of ICI-acquired pneumonias, and 60% of VAPs are late-onset.

. The predominant pathogens in VAP and HAP are gram-negative enteric organisms and staphylococci (see Table 29.1) (3). About one-quarter of the infections are polymicrobial.

. Multidrug-resistant pathogens are a growing concern, and are more likely to appear in patients who have received intravenous antibiotics in the past 90 days, in patients who are immunocompromised or receiving renal replacement therapy, and in patients with septic shock (2).

. Viruses are implicated in about 20% of cases of VAP and HAP (4). *Candida* species are common isolates in respiratory secretions, but are not known to cause pneumonia (5).

. VAP prolongs the duration of mechanical ventilation, and increases the length of stay in the ICU (5), but the impact of VAP on survival is unclear (6). Some studies show that VAP has little of no effect on mortality rate (7,8), while others show a small but significant increase in mortality rate (3).

PREVENTIVE MEASURES

Aspiration of microbes from the oropharynx is the inciting event in most cases of VAP (9). Gram-negative aerobic bacilli are the predominant pathogens in the oropharynx of ICU patients (see Figure 4.4), and they are also the predominant pathogens in VAP, as shown in Table 29.1 (3). Early cases of VAP (i.e., appear 2–4 days after intubation) are most likely caused by pathogens that are dragged into the airways during intubation.

TABLE 29.1 Common Isolates in ICU-Acquired Pneumonia

Pathogens	Early VAP[a]	Late VAP[b]	HAP[c]
Enterobacteriaceae	32%	34%	31%
P. aeruginosa	14%	20%	16%
Acinetobacter spp.	8%	21%	13%
Staphylococcus aureus	30%	21%	20%
MSSA	21%	9%	6%
MRSA	9%	13%	13%
Polymicrobial	26%	24%	21%
None identified	25%	22%	38%

From Reference 3. MSSA = methicillin-sensitive *S. aureus*, MRSA = methicillin-resistant *S. aureus.*

[a] Onset 2–4 days after intubation.

[b] Onset ≥5 days after intubation.

[c] Onset ≥48 hrs after ICU admission in non-ventilated patients.

Oral Decontamination

The discovery that pathogens in the oropharynx are the culprits in VAP led to the introduction of oral decontamination as a preventive measure for VAP. Oral decontamination is described in Chapter 4, and is briefly reviewed here.

Methods

There are two methods for eliminating pathogens from the oropharynx (see Table 4.1). The popular (but problematic) method is topical application of 0.12% chlorhexidine gluconate to the oral mucosa every 6 hours. The problem is evidence of increased mortality associated with chlorhexidine (10), which is attributed to a chlorhexidine-induced mucositis that disrupts the mucosal barrier in the mouth and leads to septicemia with pathogenic mouth organisms (11). Because of this risk, *chlorhexidine is no longer recommended for oral decontamination* in the most recent guidelines on VAP (3).

The preferred decontamination method is *selective oral decontamination* (SOD) (3), which uses nonabsorbable antibiotics applied to the oral mucosa (see Table 4.1 for an example of an SOD regimen). The aim of SOD is to "selectively" eliminate pathogens while retaining the normal microbial environment in the mouth (which presumably helps to prevent further colonization with pathogens). The success of this approach is demonstrated in Figure 29.1, which shows that SOD is associated with a significant decrease in both tracheal colonization and pneumonia in ventilator-dependent patients (12). Unfortunately, SOD has been unpopular in the United States, primarily due to the unfounded fear that SOD will promote bacterial resistance. (See Chapter 4 for more on this topic.)

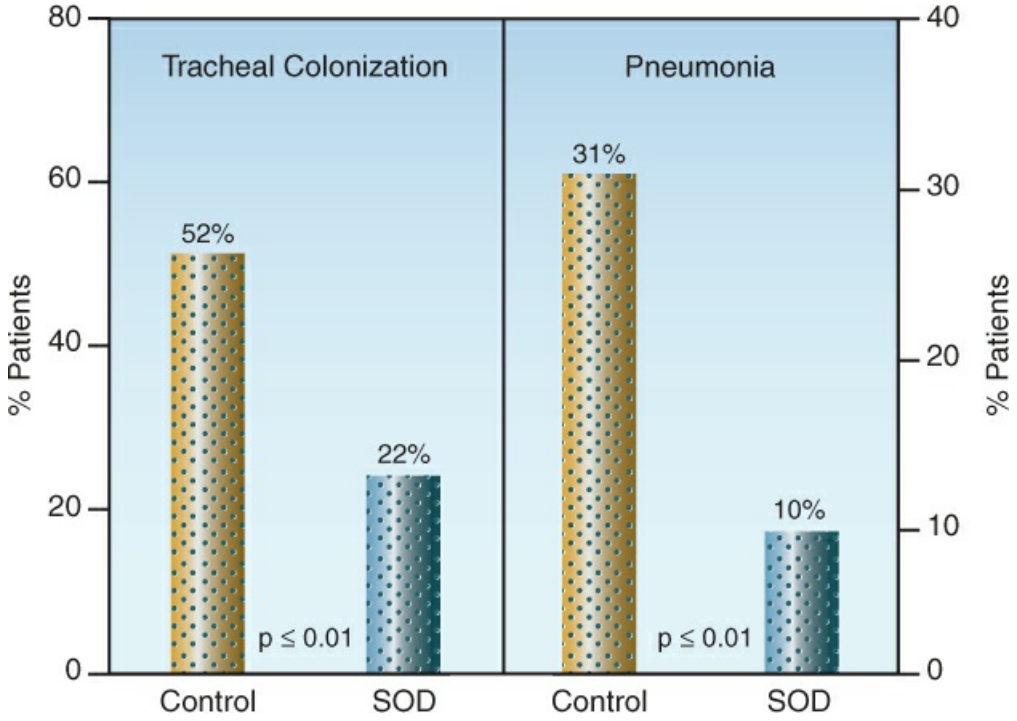

FIGURE 29.1 The effects of selective oral decontamination (SOD) on tracheal colonization and pneumonia in ventilator-dependent patients. The p value in each graph indicates a significant difference between the groups. Data from Reference 12.

The Ventilator Bundle

The Institute for Healthcare Improvement has advocated the use of "bundles" which are a collection of practices that, when used together, will improve outcomes. The bundle introduced for ventilator-dependent patients is shown in Table 29.2. Although some of the practices in this bundle do not have a direct bearing on pneumonia, its use has been shown to reduce the incidence of VAP (13), and it is sometimes called the "VAP Bundle" (14).

TABLE 29.2 The Ventilator Bundle

1. Elevate head of the bed to 30–45° above horizontal.
2. Prophylaxis for stress ulcer bleeding.
3. Prophylaxis for venous thromboembolism.

4. Daily sedation holiday.
5. Daily assessment of readiness to extubate.

The Semirecumbent Position

Elevation of the head of the bed to 30–45° (semirecumbent position) is considered an important measure for preventing gastroesophageal reflux and aspiration of gastric contents into the airways. However, while some studies have validated the benefit of the semirecumbent position (15), other studies have shown no difference in the incidence of VAP with patients in the supine and semirecumbent positions (16).

COMMENT: *Since the principal source of VAP is aspiration of pathogens in mouth secretions, elevating the head of the bed could increase the risk of VAP by promoting the movement of mouth secretions into the lungs (by gravity flow).* This has never been studied, nor is it ever mentioned in discussions of the semirecumbent position to prevent VAP.

Airway Care

As mentioned in Chapter 28, tracheal tubes serve as a nidus for pathogenic colonization and biofilm formation (see Figure 28.4), and passing a suction catheter through the tubes can dislodge these biofilms and inoculate the lungs with pathogenic organisms (17). As a result of this risk, *routine suctioning of the airways is not recommended* (18). Instead, suctioning should be performed only when there is evidence of troublesome respiratory secretions.

Subglottic Aspiration

Inflation of the cuff on tracheal tubes does not prevent aspiration of mouth secretions into the lower airways, and concern about this aspiration prompted the introduction (in 1992) of specialized endotracheal tubes equipped with a suction port just above the cuff, as shown in Figure 29.2. The section port is connected to a source of continuous suction (usually not exceeding –20 cm H_2O) to clear the secretions that accumulate in the subglottic region. Clinical studies have shown *a significant reduction in the incidence of VAP when subglottic secretions are cleared using specialized endotracheal tubes* (19).

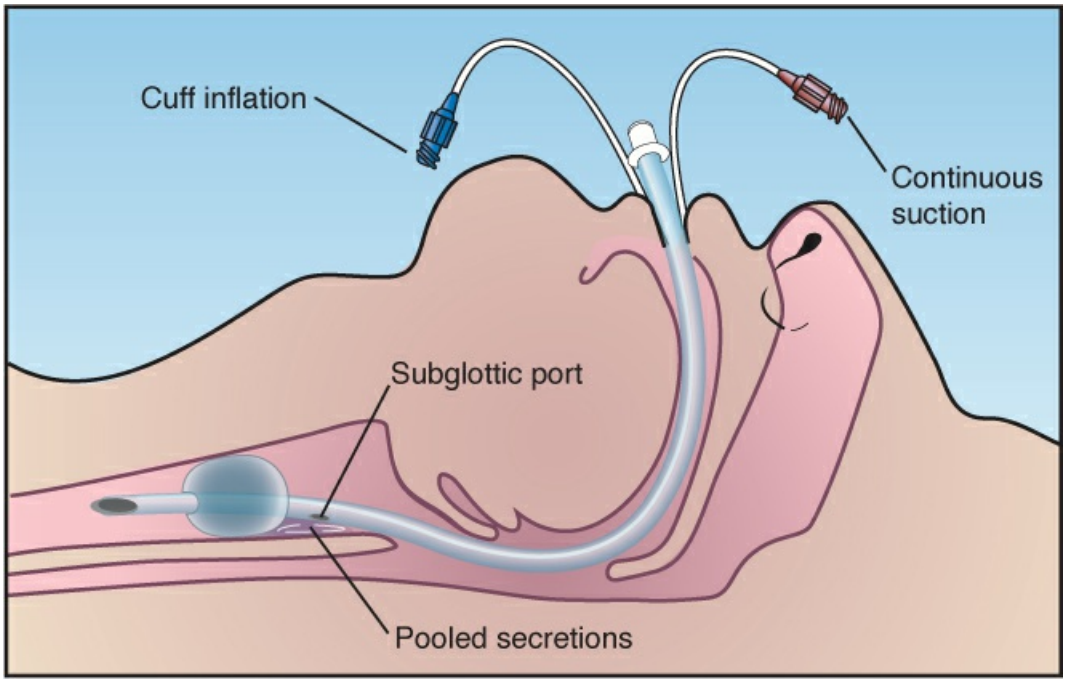

FIGURE 29.2 Endotracheal tube with a suction port placed just above the cuff to clear secretions that accumulate in the subglottic region.

CLINICAL MANIFESTATIONS

The traditional clinical criteria for the diagnosis of VAP include: (*a*) fever or hypothermia, (*b*) leukocytosis or leukopenia, (*c*), an increase in volume of respiratory secretions or a change in character of the secretions, and (*d*) a new or progressive infiltrate on the chest x-ray. The hallmark of these clinical criteria is their lack of reliability (20), as described next.

Reliability

The performance of the diagnostic criteria for VAP is shown in Table 29.3. In this case, the criteria were evaluated using cases of VAP that were diagnosed by lung biopsy (21). As indicated, none of the clinical criteria was sensitive or specific for the diagnosis of VAP, and the diagnostic odds ratio for each criterion was poor (see the legend of Table 29.3 for a description of the diagnostic odds ratio). The poor performance of these diagnostic criteria indicate that *the diagnosis of VAP is not possible using clinical criteria alone*.

TABLE 29.3 Diagnostic Value of Clinical Findings in VAP Verified by Lung Biopsy

	Sensitivity	Specificity	Diagnostic Odds Ratio†
Fever	66%	54%	2.3
Leukocytosis	64%	59%	2.6
Purulent Secretions	77%	39%	2.1

Infiltrate on Chest X-Ray	89%	26%	2.8

†The odds of a positive test in a patient with the disease relative to the odds of a positive test in a patient without the disease. A reliable test has an odds ratio of 10 or higher. Data from Reference 21.

Specificity of Chest Radiography

One of the major problems in the clinical diagnosis of VAP is the nonspecific nature of pulmonary infiltrates in ICU patients. This is indicated in Table 29.4, which shows a specificity of only 26% for radiographic infiltrates. *Pneumonia accounts for only one-third of the pulmonary infiltrates in ICU patients* (22,23), which means that conditions other than pneumonia are the most frequent cause of pulmonary infiltrates in ICU patients. The noninfectious causes of pulmonary infiltrates in the ICU include focal atelectasis, pulmonary edema, and the acute respiratory distress syndrome.

The images in Figure 29.3 demonstrate how portable chest x-rays can be misleading. Both chest x-rays in this figure were obtained within minutes of each other in the same patient. The x-ray on the left was taken after the patient exhaled in the supine position, and the x-ray on the right was obtained after the same patient inhaled in the upright position. Note the crowded lung markings at the right base in the image on the left, which were caused by the raised hemidiaphragm (from the supine position) and the relatively low lung volume (from the exhalation). In a patient with fever, this radiographic change could be mistaken for a basilar pneumonia.

MICROBIOLOGICAL EVALUATION

The diagnosis of VAP rests heavily on identifying a responsible pathogen, but there is no standardized method for collecting or culturing respiratory secretions. Blood cultures have limited value because *in cases of suspected VAP, organisms isolated in blood cultures are often from extrapulmonary sites of origin* (24). The following is a brief review of the methods used to collect and culture respiratory secretions.

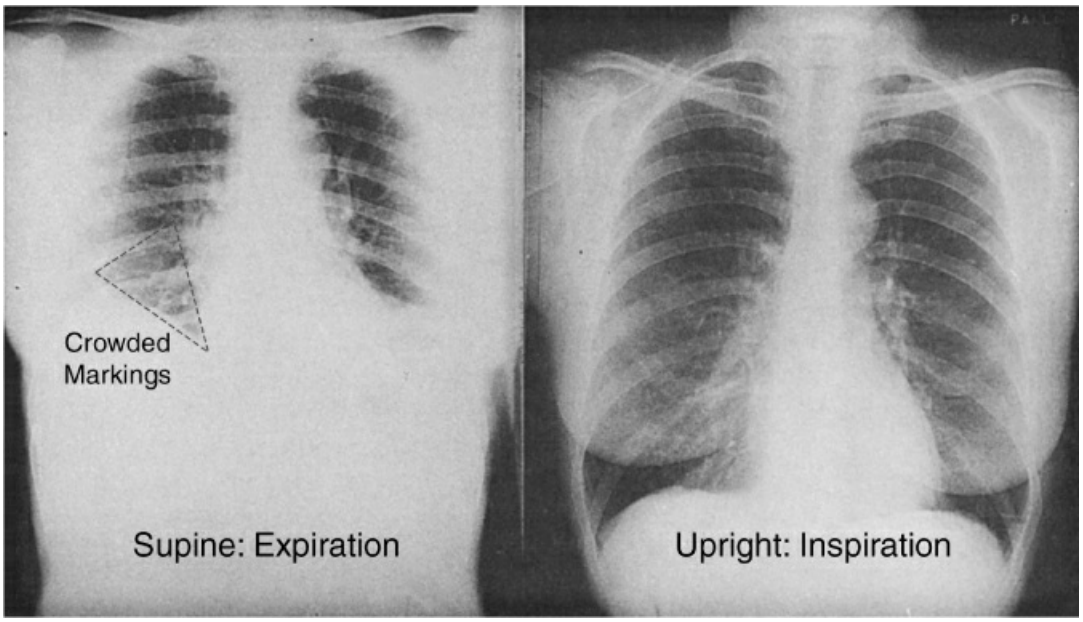

FIGURE 29.3 The effect of body position and lung volume on the appearance of a portable chest x-ray. Both images were obtained within minutes of each other in the same patient. The supine film taken after exhalation shows crowded lung markings at the right base that could be mistaken for a basilar pneumonia in a patient with a fever. Image on the left digitally enhanced.

Tracheal Aspirates

The traditional approach to suspected VAP involves aspiration of respiratory secretions through an endotracheal or tracheostomy tube, and these specimens can be contaminated with mouth secretions that are aspirated into the upper airway. A screening method to determine of the sample is appropriate for culture is described next (and should be performed routinely in the microbiology laboratory).

Microscopic Analysis

The cellular content of a tracheal aspirate is used to determine the suitability of a specimen for culture. This is explained using the sputum Gram's stain in Figure 29.4, which identifies two types of cells:

. Squamous epithelial cells, which are large, flattened cells with abundant cytoplasm and a small nucleus. These cells line the oral cavity, and *the presence of more than 10 squamous epithelial cells per low power field (×10) indicates that the specimen is contaminated with mouth secretions*, and is not an appropriate specimen for culture (25).

. Neutrophils, which are about the size of the nucleus of the epithelial cells, and have a multilobulated nucleus (which is not apparent in a low magnification view). The mere presence of neutrophils in respiratory secretions is not evidence of infection, since neutrophils can make up 20% of the cells recovered from a routine mouthwash (26). The neutrophils should be present in abundance to indicate infection; i.e., *more than 25 neutrophils per low power field (×10) is considered evidence of infection* (25). (However, this will not distinguish between tracheal bronchitis and pneumonia.)

Qualitative Cultures

The standard practice is to perform qualitative cultures on endotracheal aspirates (where the growth of organisms is reported, but there is no assessment of growth density). These cultures have a high sensitivity (usually >90%) but a very low specificity (15–40%) for identifying the culprit organism (27). This means that *for routine (qualitative) cultures of tracheal aspirates, a negative culture can be used to exclude the presence of a treatable infection, but a positive culture cannot be used as reliable evidence of the culprit organism*. The poor predictive value of positive cultures is due to contamination of tracheal aspirates with secretions from the mouth and upper airways.

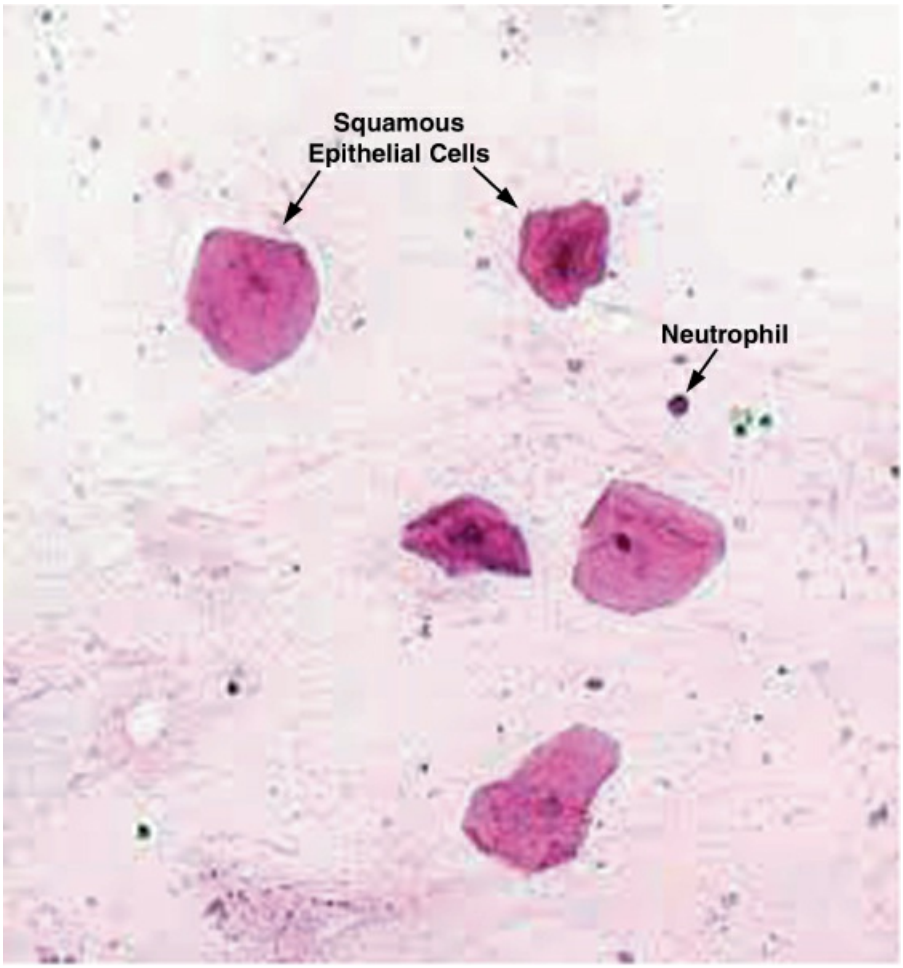

FIGURE 29.4 Sputum Gram's stain under low power magnification (×10) showing the appearance of squamous epithelial cells (from the oral cavity) and neutrophils.

Quantitative Cultures

For quantitative cultures of tracheal aspirates (where growth density is reported), the threshold for the diagnosis of VAP is 10^5 colony-forming units per mL (CFU/mL) (28). This threshold has a sensitivity of 76% and a specificity of 68% for identifying the responsible pathogen (see Table 29.4) (21). Comparing these results with routine cultures (which have a sensitivity >90% and specificity ≤40%) shows that, *for cultures of tracheal aspirates, quantitative cultures are more*

reliable for identifying the responsible pathogen.

Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL) is performed by wedging a bronchoscope in a distal airway (in a lung region where the infection is suspected) and performing a lavage with sterile isotonic saline. A minimum lavage volume of 120 mL is recommended for adequate sampling (29), which is achieved by performing a series of 6 lavages using 20 mL for each lavage (only 25% or less of the volume instilled will be returned via aspiration). The first lavage is usually discarded, and the remainder of the lavage fluid is pooled and sent to the microbiology lab for microscopic analysis and quantitative culture.

Quantitative Cultures

BAL specimens are cultured quantitatively, and the threshold for the diagnosis of VAP is 10^4 CFU/mL (28). The diagnostic performance of BAL cultures is shown in Table 29.4 (21). The diagnostic odds ratio indicates that *BAL cultures are the most reliable cultures available,* but the sensitivity and specificity indicate they are far from ideal.

TABLE 29.4 Diagnostic Value of Quantitative Cultures in VAP Verified by Lung Biopsy

	Tracheal Aspirate	Protected Brush Specimen	Bronchoalveolar Lavage
Threshold (CFU/mL)	10^5	10^3	10^4
Sensitivity	76%	61%	71%
Specificity	68%	77%	80%
Diagnostic Odds Ratio†	6.6	5.1	9.6

†The odds of a positive test in a patient with the disease relative to the odds of a positive test in a patient without the disease. A reliable test has an odds ratio of 10 or higher. Data from Reference 21.

Intracellular Organisms

Inspection of BAL specimens for intracellular organisms can help in guiding initial antibiotic therapy until culture results are available. *When intracellular organisms are present in more than 3% of the cells in the lavage fluid, the likelihood of pneumonia is over 90%* (30). This is not done on a routine Gram's stain, but requires special processing and staining, and will require a specific request to the microbiology lab.

BAL Without Bronchoscopy

BAL can also be performed without the aid of bronchoscopy using a sheathed catheter like the one illustrated in Figure 29.5. This catheter is about 50 cm in length, and is inserted through an endotracheal or tracheostomy tube and advanced "blindly" until it wedges in a distal airway. The tip of the catheter has a bioabsorbable polyethylene plug that prevents contamination while the catheter is advanced. Once wedged, an inner cannula is advanced to dislodge the plug, and the BAL is performed with 10–20 mL of sterile saline.

Nonbronchoscopic BAL (also called mini-BAL because of the lower lavage volume) is a safe procedure that can be performed by respiratory therapists (31). Despite the uncertainty about the location of the catheter tip in relation to the region of suspected infection, the yield from quantitative cultures with mini-BAL is equivalent to the yield with bronchoscopic BAL (32).

Protected Specimen Brush

Aspiration of secretions through a bronchoscope produces false-positive cultures because of contamination as the bronchoscope is advanced through the upper respiratory tract (29). To eliminate this problem, a specialized brush called a *protected specimen brush* (PSB) was developed to collect uncontaminated secretions from the distal airways during bronchoscopy. Like the mini-BAL catheter, the PSB catheter has an inner cannula and a bioabsorbable plug at the tip to prevent contamination during catheter advancement. When the catheter tip is placed in the desired location, the brush is advanced from the inner cannula to collect samples from the distal airways.

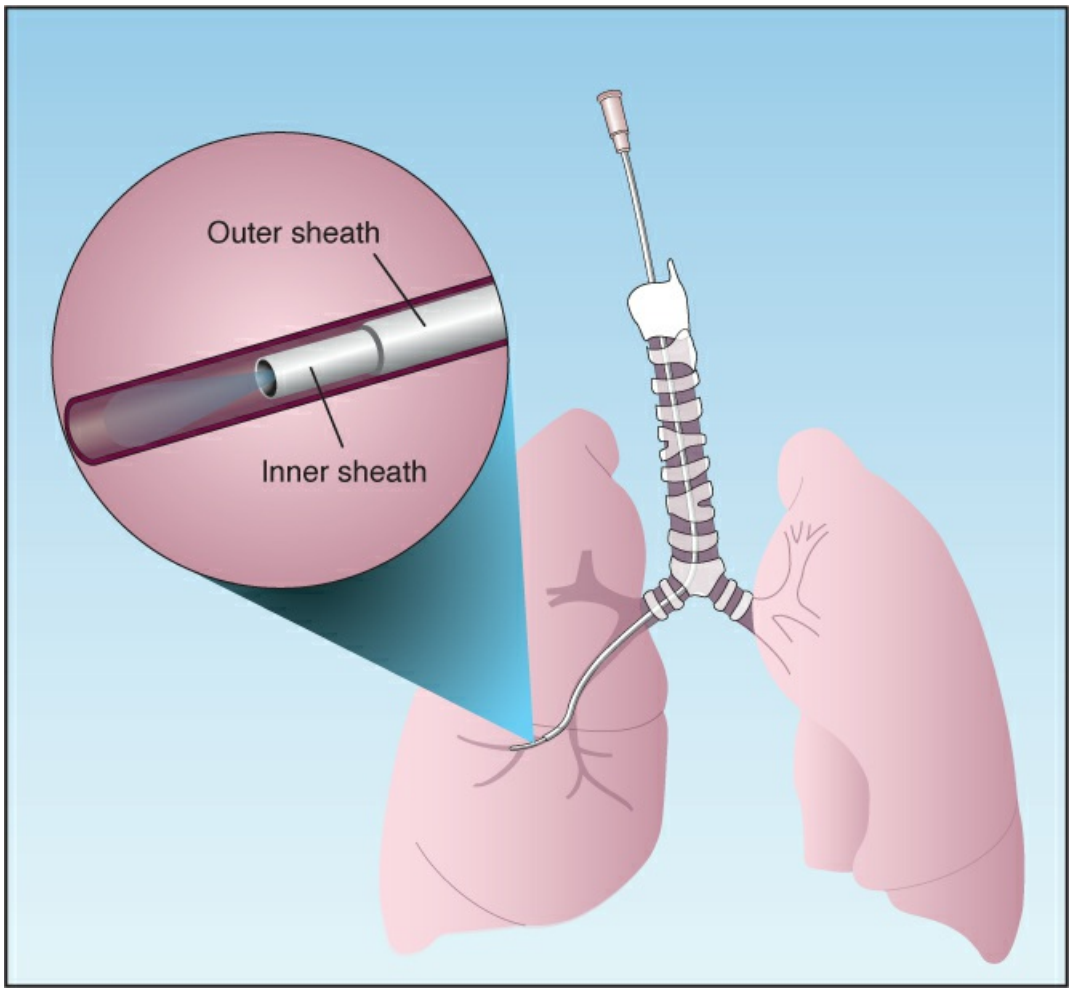

FIGURE 29.5 Protected catheter for performing bronchoalveolar lavage without the aid of bronchoscopy. See text for explanation.

Quantitative Cultures

PSB cultures are processed quantitatively, and the threshold for a positive culture is 10^3 CFU/mL (21). The diagnostic performance of PSB cultures is shown in Table 29.4 (21); as indicated by the diagnostic odds ratio, PSB cultures are less reliable than BAL cultures, but are more specific than quantitative cultures of tracheal aspirates.

Which Method is Preferred?

The clinical practice guidelines differ about the appropriate culture method: i.e.,

. The international guidelines (1) recommend quantitative cultures with BAL, mini-BAL, or PSB over cultures of tracheal aspirates, which optimizes accuracy, and reduces the number of false-positive cultures that result in overuse of antibiotics. These cultures, however, must be obtained prior to the start of empiric antibiotic therapy.

. The U.S.-based guidelines (2) recommend routine tracheal cultures over all other culture methods, based on evidence that the more invasive procedures (BAL or PSB) do not improve clinical outcomes. Once again, these cultures should be obtained prior to the start of empiric antibiotic therapy.

Take your pick, although it seems that the culture methods with the best performance characteristics (i.e., BAL cultures) should be preferred, and using mini-BAL would avoid the extra cost of bronchoscopy.

PARAPNEUMONIC EFFUSIONS

Pleural effusions are present in 20–40% of pneumonias in hospitalized patients (33). These *parapneumonic effusions* can be evident on chest x-ray, although ultrasound is recommended to define the location and size of the effusion (34), especially if thoracentesis is performed.

Classification

Parapneumonic effusions can be placed in 4 categories of increasing severity. These are outlined in Table 29.5 (33).

TABLE 29.5 Classification of Parapneumonic Effusions

	Character of Effusion	Pleural Fluid Analysis	Chest Tube
Category 1	<10 mm in thickness	Thoracentesis not necessary	No
Category 2	>10 mm thick but <50% of hemithorax, free-flowing.	pH >7.20, Glucose >60 mg/dL, negative Gram's stain & culture.	No
Category 3	Loculated, or fills >50% of hemithorax.	pH <7.20, Glucose <60 mg/dL, positive Gram's stain or culture.	Yes
Category 4	Purulent	Same as Category 3	Yes

From Reference 33.

Category 1

Category 1 effusions are small (<10 mm on decubitus films, CT images, or ultrasound), and are free-flowing. No thoracentesis is required, unless the patient's clinical condition deteriorates and the effusion increases in size (see next).

Category 2

Category 2 effusions are small-to-moderate in size (>10 mm thickness, but fill less than one-half the hemithorax) and are free-flowing. Thoracentesis is advised, and as much fluid as possible should be removed. (*Note:* Some advise measuring the pleural pressure with a manometer during pleural drainage, and stopping the drainage if the pleural pressure reaches –20 cm H_2O, to prevent negative-pressure pulmonary edema) (34). Pleural fluid analysis in category 2 effusions shows no evidence of infection: i.e., the pleural fluid pH is >7.20, the glucose is >60 mg/dL, and the Gram's stain and culture are negative. No other intervention is needed for these effusions.

Category 3

Category 3 effusions (are also called "complicated effusions") are either loculated, or they fill more than one-half of the hemithorax, and pleural fluid analysis reveals evidence of infection: i.e., the pH is <7.20, the glucose is <60 mg/dL, and the Gram's stain and/or culture is positive. Pleural drainage is required for these effusions, using small-bore (8.5–14 French) chest tubes.

Category 4

Category 4 effusions are empyemas; i.e., the pleural fluid is grossly purulent. Immediate pleural drainage is essential. Some prefer large (28–36 French) chest tubes for draining pus, but small bore (8.5–14 French) tubes achieve drainage that is equivalent to the larger tubes (35).

Antibiotics

Pleural drainage of infected parapneumonic effusions should be combined with empiric antibiotic therapy. For parapneumonic effusions in hospitalized patients, empiric coverage should include methicillin-resistant *Staphylococcus aureus*, and gram-negative enteric organisms, including *Pseudomonas aeruginosa* (36). A suitable regimen would be vancomycin plus cefepime or piperacillin/tazobactam.

Ineffective Drainage

Loculated effusions can be difficult to drain. If drainage is inadequate with the initial chest tube, an additional tube can be placed (preferably under CT guidance). Further problems with drainage should prompt a surgical consult for *video-assisted thoracoscopic surgery* (VATS), which can disrupt the pleural adhesions without a thoracotomy. The intrapleural administration of fibrinolytic agents is generally not advised for complicated parapneumonic effusions and empyema (36,37).

ANTIMICROBIAL THERAPY

Prompt administration of empiric antibiotics is recommended for all cases of suspected VAP.

The antibiotic regimen is determined by the risk factors described next.

Risk Factors

The risk factors for an unfavorable outcome include all of the following (1,2): (*a*) late-onset VAP, (*b*) septic shock, (*c*) prior infection with methicillin-resistant *Staphylococcus. aureus* (MRSA) or a multidrug-resistant organism (i.e., resistant to at least two different classes of antibiotics), (*d*) a hospital microbiogram in which 25% of the isolates are resistant organisms, and (*e*) antibiotic exposure in the past 90 days.

Empiric Regimens

The recommended empiric regimens for low-risk and high-risk patients are outlined in Table 29.6 (1,2), and are briefly summarized below.

Low-Risk Regimen

Early-onset cases of VAP without septic shock or any of the other risk factors just mentioned can be treated with a single agent that covers methicillin-sensitive *Staphylococcus aureus* (MSSA), gram-negative enteric organisms, and *Pseudomonas aeruginosa* (1,2). Candidates include cefepime, levofloxacin, and piperacillin/tazobactam.

High-Risk Regimen

The high-risk empiric regimen includes coverage for MRSA (with vancomycin or linezolid) and antipseudomonal coverage with a β-lactam antibiotic (cefepime, levofloxacin, or piperacillin/tazobactam). If there is a high index of suspicion for a multidrug-resistant organism, additional gram-negative and antipseudomonal coverage is recommended using a non-β-lactam agent (a fluoroquinolone or an aminoglycoside) (1).

There is a tendency to continue empiric antibiotics despite negative culture results if patients are improving, but this is not justified, and antibiotics should be discontinued if all cultures are unrevealing.

TABLE 29.6 Empiric Antibiotic Regimens for Suspected VAP

Low Risk Patients	High Risk Patients
A. MSSA and gram-negative (including antipseudomonal) coverage with any of the following: 1. Cefepime 2. Levofloxacin 3. Piperacillin/Tazobactam	A. MRSA coverage with: 1. Vancomycin or 2. Linezolid B. Gram-negative and antipseudomonal coverage with a β-lactam agent: 1. Piperacillin/Tazobactam or 2. Cefepime or 3. Meropenem C. Gram-negative and antipseudomonal coverage with a non-β-lactam agent:§ 1. Levofloxacin or 2. An aminoglycoside

§Include regimen C only if there is a high risk of infection with multidrug-resistant organisms.

MSSA = methicillin-sensitive *S. aureus*. Recommendations from References 1 and 2.

Treatment of Documented Pneumonia

Antibiotic therapy of documented VAP will be dictated by the sensitivities of the isolated pathogen(s). The recommended duration of antibiotic therapy is 7 days (1,2).

A FINAL WORD

The Mortality Risk with VAP

As mentioned early in this chapter, a number of studies have shown that VAP has little or no impact on mortality rates (6–8). This observation suggests one of the following scenarios:

. We're really good at treating VAPs.

. VAPs are not life-threatening infections.

. VAPs are overdiagnosed.

Recalling the lack of specificity in the diagnostic criteria for VAP (see Tables 29.3 and 29.4), it seems that the third choice is the most appropriate.

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Chapter 30

Discontinuing Mechanical Ventilation

The spirit indeed is willing, but the flesh is weak.

Matthew 26:41

Discontinuing mechanical ventilation (popularly known as *weaning* from mechanical ventilation) is often a rapid and uneventful affair, but about one of every three patients experience difficulties in the transition to unassisted breathing (1). This chapter describes the process of removing patients from mechanical ventilation, and the problems that can arise. The most recent clinical practice guidelines on this process are included in the bibliography at the end of the chapter (2–4).

VENTILATOR STRATEGIES

Attention to the following issues during mechanical ventilation can facilitate the transition to spontaneous breathing.

Patient-Triggered Breaths

The diaphragm is an involuntary muscle that contracts whenever we take a breath, and this continues as long as there is a central drive to breathe. However, mechanical ventilation can promote diaphragm weakness (5), and this *ventilator-induced diaphragm dysfunction* is particularly prominent during controlled ventilation, when the patient is not allowed to initiate a ventilator breath. This is demonstrated in Figure 30.1, which is from an animal study that compared the force of diaphragmatic contractions during spontaneous breathing, and after 3 days of assisted ventilation (where each ventilator breath was initiated by a breathing effort) or controlled ventilation (where there were no breathing efforts) (6). In this case, controlled ventilation is associated with a significant (~50%) reduction in the force of diaphragmatic contractions at each frequency tested.

Observations like those in Figure 30.1 indicate that allowing patients to trigger ventilator breaths (e.g., by avoiding neuromuscular paralysis or heavy sedation) will help to preserve the strength of the diaphragm, and should facilitate the transition from ventilatory support to spontaneous breathing. (The role of diaphragm weakness in weaning from the ventilator is

described later in the chapter.)

Physiotherapy

Prolonged bed rest and physical inactivity leads to deconditioning and generalized muscle weakness, and this is considered a contributing factor in difficulties weaning from mechanical ventilation. A program of progressive physiotherapy (e.g., sitting on the edge of the bed, standing, and ambulation) has been shown to facilitate weaning from mechanical ventilation (7), and protocolized physiotherapy is recommended for all ventilator-dependent patients who are otherwise clinically stable (2).

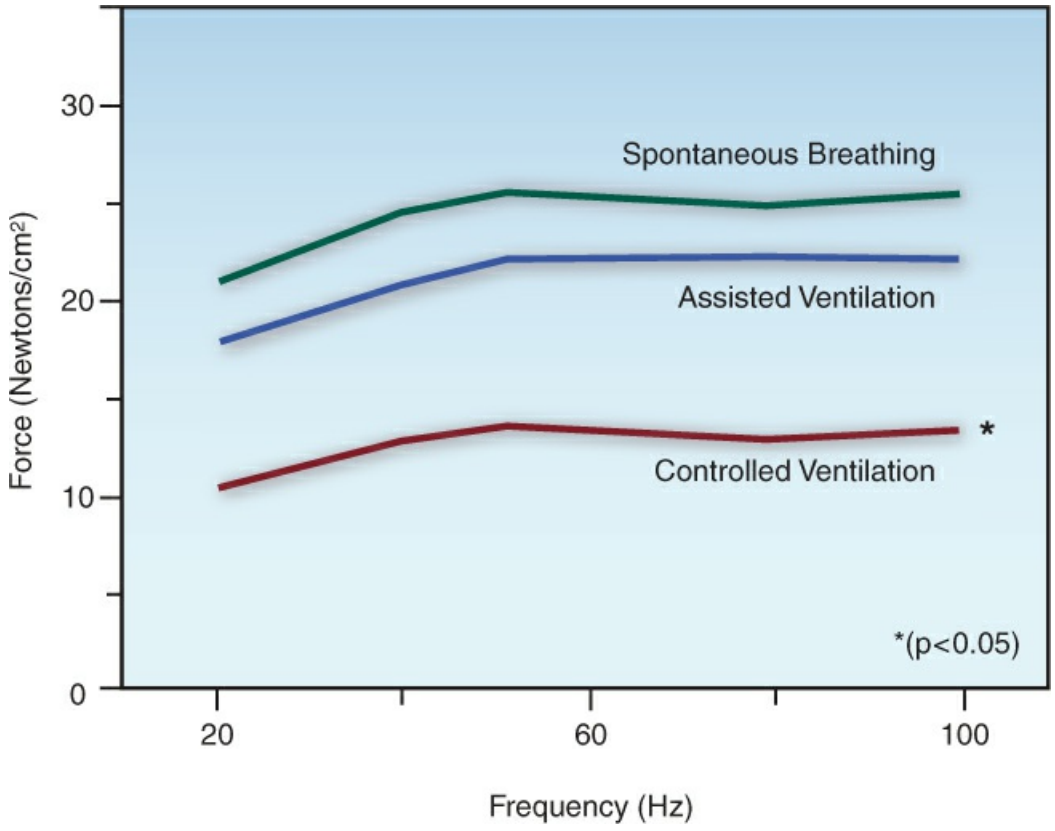

FIGURE 30.1 The force of diaphragmatic contractions at various stimulation frequences during spontaneous breathing and after 3 days of assisted ventilation (where each ventilator breath is initiated by an inspiratory effort) and controlled ventilation (where there are no spontaneous breathing efforts). Data from Reference 6.

Sedation Practices

Deep sedation (where the patient is not arousable) and sustained use of benzodiazepines (especially midazolam) will delay awakening (8), and this delays the liberation from mechanical ventilation (8). As a result, the most recent guidelines on sedation in ventilator-dependent patients (9) includes the following recommendations:

. Maintain a light level of sedation, where patients are easily aroused.

. Consider daily “sedation holidays” to prevent the accumulation of sedative agents.

. Avoid or minimize the use of benzodiazepines for sedation.

For more on sedation during mechanical ventilation, see Chapter 6.

THE SPONTANEOUS BREATHING TRIAL

Readiness

The management of ventilator-dependent patients requires constant vigilance for signs that the patient is ready for a trial of spontaneous breathing. These "readiness criteria" are listed in the left-hand column in Table 30.1. Suitable candidates should have adequate arterial oxygenation (i.e., SpO_2 ≥90%) while breathing non-toxic concentrations of oxygen (FIO_2 ≤50%) at low levels of PEEP (≤8 cm H_2O), and should have an arterial PCO_2 that is normal or at baseline levels. Patients should also be hemodynamically stable and either awake or arousable and cooperative.

TABLE 30.1 Parameters for a Spontaneous Breathing Trial

Readiness Criteria	Predictors of Success†
1. SpO_2 ≥90% with FIO_2 ≤50%	1. Tidal volume (V_T) 4–6 mL/kg (PBW)
2. PEEP ≤8 cm H_2O	2. Respiratory rate (RR) <40 /min
3. $PaCO_2$ normal or at baseline	3. RR / V_T Ratio = 60–105 bpm/L
4. Hemodynamically stable	4. Max Insp Pressure > −20 cm H_2O
5. Arousable & Cooperative	

†Measurements obtained during spontaneous breathing. PBW = predicted body weight.

When the readiness criteria are satisfied and the spontaneous breathing trial begins, the measurements listed in the right hand column of Table 30.1 can help to determine if spontaneous breathing will be successful (10). Each of these parameters can be a poor predictor of success or failure in individual patients, but when taken together, they will give you a good idea of how things will proceed. Serial changes in these measurements have more predictive value than spot measurements obtained at the onset of the spontaneous breathing trial (11).

Methods

There are two methods for a spontaneous breathing trial (SBT), as described next.

Using the Ventilator Circuit

The popular method of conducting SBTs is to leave the patient connected to the ventilator. The advantage of this method is the ability to monitor the tidal volume (V_T) and respiratory rate (RR), since rapid, shallow breathing (indicated by an increase in the RR/V_T ratio) is a common breathing pattern in patients who fail the SBT (9).

To counteract the resistance to breathing through the ventilator circuit, low levels of pressure support (5 cm H_2O) are routinely employed. (For a description of pressure support ventilation, see Chapter 26, and Figure 26.2.) However, as demonstrated in Figure 30.2, *the use of pressure*

support does not significantly reduce the work of breathing (12), which is consistent with studies showing that the addition of pressure support does not facilitate weaning from mechanical ventilation (13).

The T-Piece Circuit

SBTs can also be conducted when the patient is disconnected from the ventilator, using the simple circuit design illustrated in Figure 30.3. A source of O_2 (usually from a wall outlet) is delivered to the patient at a high flow rate (higher than the patient's inspiratory flow rate), and this not only facilitates the inhalation of O_2, it also carries exhaled CO_2 out to the atmosphere, to prevent CO_2 rebreathing. Because this circuit employs a T-shaped adapter, this type of SBT is popularly known as a "T-piece trial".

The T-piece circuit uses high flow rates, and thus may be better suited for patients with high ventilatory demands (although this is unproven). The major disadvantage of the T-piece circuit is the inability to monitor the respiratory rate and tidal volume.

Which Method is Preferred?

There is no clinically proven advantage with any method for SBTs (13,14), which means that when a patient is ready to resume spontaneous breathing, it doesn't matter how you do it. Leaving the patient attached to the ventilator during SBTs is favored because it is easier to set up.

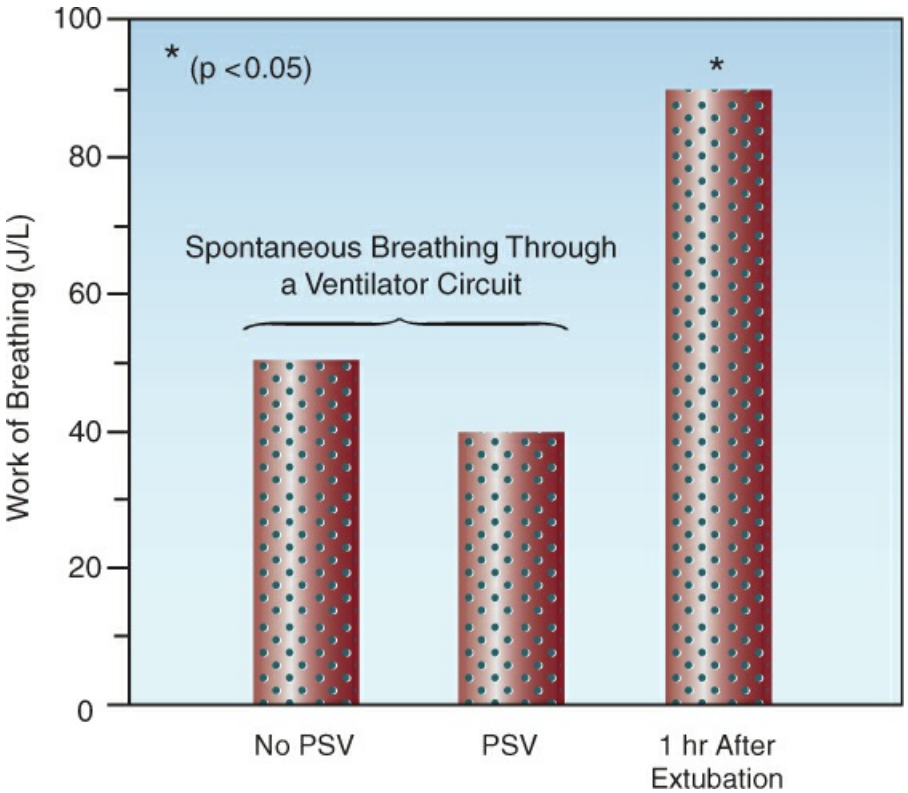

FIGURE 30.2 The work of breathing (in joules per liter) during spontaneous breathing trials conducted with and without the aid of pressure support ventilation (PSV) at 5 cm H_2O, and one hour after extubation. The asterisk indicates a significant difference at the p = 0.05 level. Data

from Reference 12.

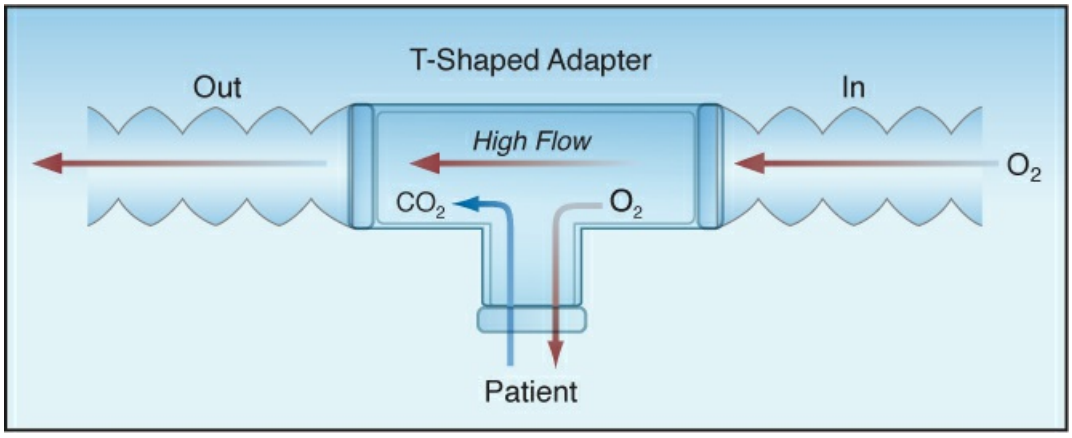

FIGURE 30.3 The T-piece circuit used for spontaneous breathing trials. The O_2 is delivered at high flow rates, which facilitates both O_2 inhalation and CO_2 removal.

Success vs. Failure

Success or failure of an SBT is judged by one or more of the following:

. Signs of respiratory distress: i.e., agitation, diaphoresis, rapid breathing, and use of accessory muscles of respiration.

. Signs of respiratory muscle weakness: e.g., paradoxical inward movement of the abdominal wall during inspiration.

. Adequacy of gas exchange in the lungs; e.g., arterial O_2 saturation, PaO_2/FIO_2 ratio, and arterial PCO_2.

. Adequacy of systemic perfusion, as assessed by the central venous O_2 saturation.

The time allotted for an SBT trial varies from less than 30 minutes to longer than 2 hours, depending on the clinical condition of the patient. A majority of patients (~80%) who tolerate SBTs for 2 hours can be permanently removed from the ventilator (10).

Rapid Breathing

Rapid breathing during SBTs is a common source of concern, but tachypnea may be a sign of anxiety rather than ventilatory failure (15). Monitoring the tidal volume can be useful in distinguishing anxiety from ventilatory failure; i.e., *anxiety produces hyperventilation*, where the respiratory rate and tidal volume are both increased, whereas ventilatory failure usually produces rapid and shallow breathing, where the respiratory rate is increased but the tidal volume is decreased. Therefore, *for the patient who develops rapid respirations during a trial of unassisted breathing, an increased tidal volume suggests anxiety as the underlying problem, while a decreased tidal volume suggests ventilatory failure*. Worsening of gas exchange may not distinguish between anxiety and ventilatory failure for the reasons described next.

Adverse Effects

Regardless of the cause, rapid breathing during SBTs can be detrimental in several ways, as summarized below.

- In patients with asthma and COPD, rapid breathing promotes hyperinflation and intrinsic PEEP, which can: (*a*) decrease the cardiac output, (*b*) increase dead space ventilation, (*c*) decrease lung compliance, and (*d*) produce diaphragm dysfunction by flattening the diaphragm.
- For patients with infiltrative lung disease (e.g., ARDS), rapid breathing reduces ventilation in diseased lung regions (where time constants for alveolar ventilation are prolonged), and this promotes alveolar collapse and hypoxemia.
- For all patients with acute respiratory failure, rapid breathing can increase whole-body O_2 consumption, which places an added burden on systemic O_2 transport.

Management

If ventilatory failure is suspected as the cause of rapid breathing, the patient should be placed back on the ventilator. If anxiety is suspected as the culprit, administration of a sedative drug should be considered. *Opiates are particularly effective in curbing the sensation of dyspnea* (16), and should be preferred in this setting. Despite the fear of opiate use in patients with COPD, opiates have been used safely for relief of dyspnea in patients with severe COPD (16).

FAILURE OF SPONTANEOUS BREATHING

A failed trial of spontaneous breathing is usually a sign that the pathologic condition requiring ventilatory support needs further improvement. However, there are other conditions that create difficulties in discontinuing mechanical ventilation, and the principal ones are described next.

Cardiac Dysfunction

Cardiac dysfunction has been identified in 40% of failed weaning trials (17). Potential sources of cardiac dysfunction in this situation include: (*a*) negative intrathoracic pressures, which increase left ventricular afterload (see Figure 26.8), (*b*) occult PEEP, which reduces venous return to the heart, (*c*) a decrease in ventricular distensibility (18) from hyperinflation and occult PEEP, and (*d*) silent myocardial ischemia (19).

The adverse effects of cardiac dysfunction include pulmonary congestion, and a decrease in the contractile strength of the diaphragm (20). The influence of cardiac output on the strength of diaphragmatic contractions is explained by the fact that the diaphragm (like the heart) maximally extracts O_2 under normal conditions, and thus is highly dependent on the cardiac output for its O_2 supply.

Monitoring

The following approaches can be used to detect cardiac dysfunction in patients who fail repeated attempts at discontinuing mechanical ventilation.

PULMONARY ARTERY CATHETER: Although rarely used, the pulmonary artery catheter would be

useful for detecting weaning-induced increases in pulmonary capillary pressure and decreases in cardiac output.

CARDIAC ULTRASOUND: Cardiac ultrasound is a useful tool for detecting changes in systolic and diastolic function during failed trials of spontaneous breathing (19,21).

CENTRAL VENOUS O_2 SATURATION: A decrease in cardiac output is accompanied by a compensatory increase in peripheral O_2 extraction and a subsequent decrease in venous O_2 saturation. (See Chapter 9 for a description of the factors that influence venous O_2 saturation.) Therefore, a decrease in central venous O_2 saturation ($ScvO_2$) during a failed SBT could signal the appearance of cardiac dysfunction. The changes in *mixed* venous O_2 saturation (SvO_2) during successful and failed trials of spontaneous breathing are shown in Figure 30.4 (22). The SvO_2 decreased during the failed trials but not during the successful trials, suggesting that a decrease in cardiac output may be responsible for the failure to sustain spontaneous breathing. (*Note:* The $ScvO_2$ will mimic the behavior of the SvO_2.)

Management

There is surprisingly little information on methods for correcting the cardiac dysfunction that develops during spontaneous breathing trials, but the following interventions should be considered:

CPAP: Patients who develop systolic dysfunction should benefit from continuous positive airway pressure (CPAP), which promotes cardiac output by canceling the afterload-increasing effect of negative intrathoracic pressure (23,24). Since CPAP is delivered noninvasively, it will not prevent the removal of mechanical ventilation, including extubation.

DIURESIS: Patients with systolic dysfunction and an enlarged left ventricle (i.e., an increased left ventricular end-diastolic volume) or weaning-induced pulmonary edema, can benefit from diuresis (21,25). However in the absence of pulmonary edema, the judicious use of diuretics is advised for patients with concomitant right heart failure.

NITRATES: For patients who develop cardiac dysfunction associated with hypertension during an SBT, intravenous nitroglycerin (titrated to the desired blood pressure) has proved successful in removing patients from the ventilator (26).

Respiratory Muscle Weakness

Respiratory muscle weakness is always near the top of the list for potential causes of difficulty in removing ventilatory support. The following are some potential sources of respiratory muscle weakness in ventilator-dependent patients.

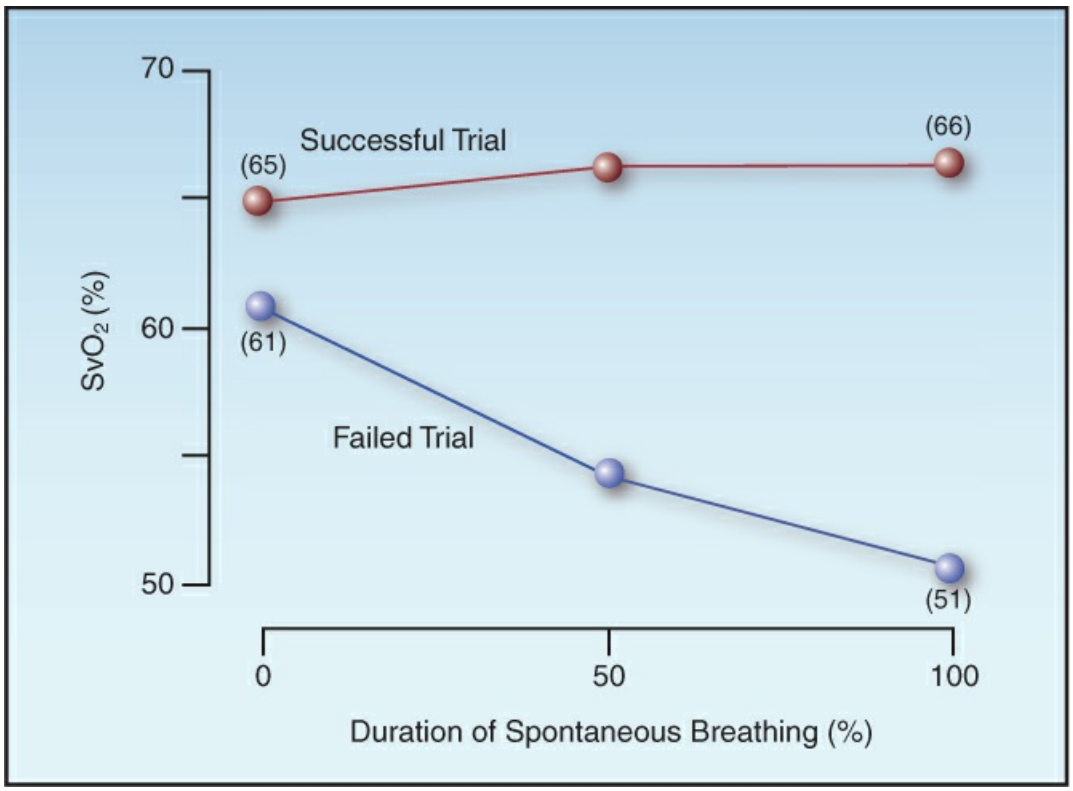

FIGURE 30.4 Mixed venous O_2 saturation (SvO_2) during successful and failed trials of spontaneous breathing. Data from Reference 22.

Potential Sources

MECHANICAL VENTILATION: As mentioned earlier (and shown in Figure 30.1), mechanical ventilation can cause diaphragm weakness when patients are not allowed to trigger ventilator breaths.

CRITICAL ILLNESS NEUROMYOPATHY: The condition known as *critical illness neuromyopathy* is an inflammatory injury to peripheral nerves and/or skeletal muscle that appears in critically ill patients, and is often recognized only when patients fail to wean from mechanical ventilation (27). This condition is described in more detail in Chapter 46. There is no effective treatment.

ELECTROLYTE DEPLETION: Magnesium and phosphorous depletion can promote respiratory muscle weakness (28,29), but the clinical relevance of this effect is unproven. Nevertheless, deficiencies in these electrolytes should be corrected in patients who fail attempts to discontinue mechanical ventilation.

Monitoring

In the supine position, diaphragm weakness can be detected by inward movement of the abdomen during inspiration, but there are few quantitative measures of diaphragm strength that are clinically applicable. (Measures such as transdiaphragmatic pressure and response to phrenic nerve stimulation are not routinely available, and are not described here.)

MAXIMUM INSPIRATORY PRESSURE: The standard clinical measure of respiratory muscle strength is the maximum inspiratory pressure (PI_{max}), which is the negative pressure that is generated by a maximum inspiratory effort against a closed airway. The normal values of PI_{max} vary widely, but mean values of –120 cm H_2O and –84 cm H_2O have been reported for adult men and women, respectively (30). Ventilation at rest is threatened when the PI_{max} drops to –20 or –30 cm H_2O, which is at the threshold for predicting the success of spontaneous breathing trials (see Table 30.1). Patients with acute respiratory failure often have difficulty performing the maneuver needed to measure PI_{max}, which limits its value is assessing diaphragm weakness in the ICU.

ULTRASOUND: Ultrasound measures of diaphragm thickness and diaphragm excursion have been proposed as measures of diaphragm dysfunction in ICU patients (31), but this methodology is limited by the lack of standardized reference measurements and the paucity of sonographers skilled in diaphragm imaging. Furthermore, the impact of this imaging on weaning from the ventilator is unclear.

Management

The management of respiratory muscle weakness is limited to physiotherapy and general supportive care (nutrition, etc.).

EXTUBATION

Once there is evidence that mechanical ventilation is no longer necessary, the next step is to remove the artificial airway. This section focuses on removing endotracheal tubes, although some of the principles also apply to removing tracheostomy tubes. (The removal of tracheostomy tubes is a more gradual process, and often occurs after patients leave the ICU.) Extubation should never be performed to reduce the work of breathing (in patients who are experiencing some respiratory distress during weaning), because the work of breathing can actually *increase* after extubation, as demonstrated in Figure 30.2. (This can be the result of an increased respiratory rate or breathing through a narrowed glottis, but it occurs in patients who tolerate extubation, so it is not necessarily a cause for concern.)

The considerations that must be addressed prior to extubation include: (*a*) the patient's ability to clear secretions from the airways, and (*b*) the risk of symptomatic laryngeal edema following extubation.

Airway Protective Reflexes

The ability to protect the airway from aspirated secretions is determined by the strength of the gag and cough reflexes. Cough strength can be assessed by holding a piece of paper 1–2 cm from the end of the endotracheal tube and asking the patient to cough. If wetness appears on the paper, the cough strength is considered adequate (32). Diminished strength or even absence of cough or gag reflexes will not necessarily prevent extubation, but will identify patients who at risk of aspiration. These patients deserve special attention aimed at swallowing function post-extubation.

Laryngeal Edema

Trauma to the larynx from the insertion and presence of endotracheal tubes can lead to laryngeal edema and upper airway obstruction after extubation. The reported incidence of laryngeal edema that is severe enough to warrant reintubation is 1–10% (33), and contributing factors include difficult and prolonged intubation, large tube size, and unplanned self-extubation.

The Cuff-Leak Test

The cuff-leak test is designed to determine the risk of upper airway obstruction from laryngeal edema after the endotracheal tube is removed. The test is performed while the patient is receiving ventilator breaths. The cuff on the endotracheal tube is deflated, which normally causes air to leak out of the lungs, and the volume of the air leak can be measured as the difference between the inhaled and exhaled volumes. (This test is best performed during volume-controlled ventilation, where the inflation volume is pre-selected.) The absence of an air leak when the cuff is deflated is then considered evidence of an upper airway obstruction from laryngeal edema.

PROBLEMS: The cuff leak test was developed for extubating children with croup (34), and the value of the test in adults has been debated for years. One of the problems is defining a negative test (i.e., evidence that upper airway obstruction is unlikely), since some studies use the presence of an auditory leak as a negative test, while other studies use a specified volume of gas that is leaked (typically 100–110 mL) as a negative test. The other problem has been the limited predictive value of positive and negative tests for identifying troublesome laryngeal edema post-extubation (32,35).

RECOMMENDATION: The cuff test should be reserved for patients that are high-risk for post-extubation laryngeal edema (e.g., those with prolonged or difficult intubations). Based on a recent study in this patient population (35), the following recommendations are reasonable:

. A leak volume >110 mL eliminates the risk of post-extubation laryngeal edema with about 95% certainty, and nothing further is needed prior to extubation.

. A leak volume <110 mL increases the risk of post-extubation laryngeal edema 7-fold, and these patients should receive pretreatment with steroids prior to extubation. They should also be placed on noninvasive ventilation immediately after extubation.

Pretreatment with Steroids

There is evidence that pretreatment with intravenous corticosteroids reduces the risk of post-extubation laryngeal edema (36,37). This is demonstrated in Figure 30.5, which is from a large, multicenter study showing that intravenous methylprednisolone (20 mg every 4 hours, with the first dose given 12 hours prior to a planned extubation) was associated with marked reductions in post-extubation laryngeal edema and in the reintubation rate (36). *Steroid pretreatment must begin hours before the extubation*, since the effect is not present if steroids are administered close to the time of extubation (38).

Noninvasive Ventilation

Noninvasive ventilation (which is described in Chapter 26) is effective in reducing the rate of

reintubation when used immediately after extubation, in patients with a high risk of laryngeal edema (39). However, similar success has not been demonstrated when post-extubation respiratory failure is established (40). Therefore, noninvasive ventilation should be used immediately after extubation in high-risk patients, and is not recommended once respiratory failure is established.

Post-extubation Stridor

The characteristic sign of upper airway obstruction from laryngeal edema is noisy breathing, also called *stridorous breathing*, or simply *stridor*, which is first apparent when the obstruction reaches about 50% (33). The sounds may be high-pitched and wheezy, or low-pitched and harsh, but they are always audible without a stethoscope, and they are *always most apparent during inspiration*. This inspiratory prominence is due to the extrathoracic location of laryngeal obstruction: i.e., negative intrathoracic pressures generated during a spontaneous inspiration are transmitted to the upper airways outside the thorax, and this results in a narrowing of the extrathoracic airways (including the larynx and pharynx) during the inspiratory phase of breathing. (In contrast, the intrathoracic airways narrow during expiration.)

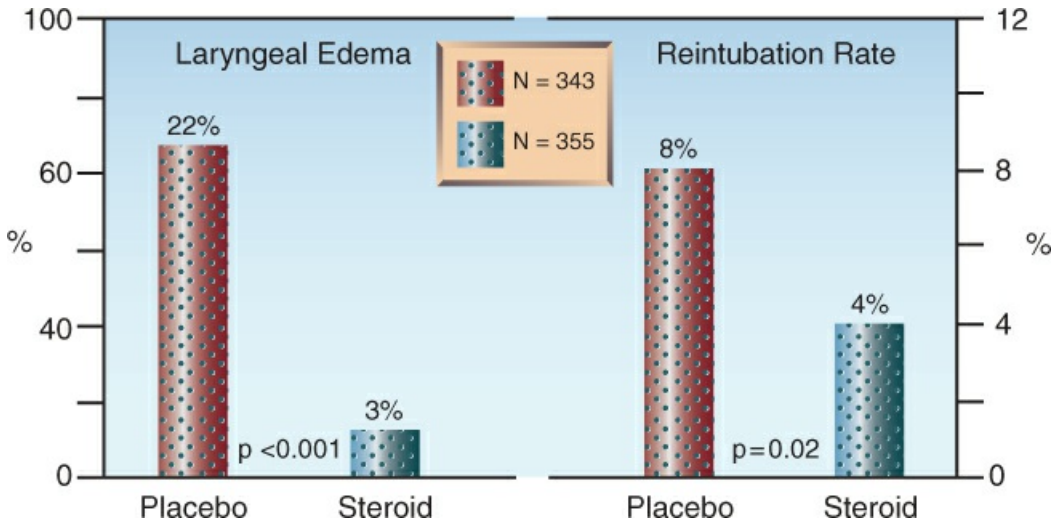

FIGURE 30.5 Results of a large, multicenter study showing that pretreatment with methylprednisolone (20 mg IV every 4 hrs, starting 12 hours prior to extubation) was associated with a 7-fold drop in the incidence of post-extubation laryngeal edema, and a 50% decline in the reintubation rate. Data from Reference 36.

Management

Post-extubation stridor is apparent within 30 minutes of extubation in most cases (32), but delays of up to 2 hours can occur (personal observation). Reintubation is not always necessary, but *any signs of impending respiratory failure (O_2 desaturation, rapid breathing) should prompt immediate reintubation*, because delays to reintubation can make it difficult to re-establish a stable airway. Furthermore, *there are no proven treatments for post-extubation laryngeal edema* (33).

Popular but unproven treatments for post-extubation laryngeal edema include nebulized epinephrine and intravenous steroids. Since there is no evidence that either of these interventions is effective, it is not possible to recommend an effective dosage.

A FINAL WORD

Avoiding Delays

One of the most important aspects of discontinuing mechanical ventilation is to avoid unnecessary delays, and the following measures should help in this regard.

. Keep sedation as light as possible.

. Start physiotherapy as soon as the patient is clinically stable.

. Be attentive to the patient's nutritional status.

. Be vigilant for signs that the patient is ready for a spontaneous breathing trial, and extubate the patient in a timely fashion if the trial is successful.

. Don't forget the possible role of the heart in failed trials of spontaneous breathing.

. If concerned about post-extubation laryngeal edema, pretreat with steroids prior to extubation, and extubate the patient to noninvasive positive pressure breathing.

These measures should help to free patients from mechanical ventilation, and end the misfortune of being tethered to a machine.

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Section X

ACID-BASE DISORDERS

To do common things perfectly is far better worth our endeavor than to do uncommon things respectably.

Harriet Beecher Stowe
(1864)

Chapter 31

Acid-Base Analysis

Seek simplicity, and distrust it.

Alfred North Whitehead (*a*)

Acid-base physiology and pathology is one of the fundamental knowledge bases in the care of acutely ill patients, and mastery is required for the management of critically ill patients. This chapter presents a structured approach to the identification of acid-base disorders based on the relationships between the pH, PCO_2 and bicarbonate (HCO_3) concentration in extracellular fluid (plasma). Much of this information will be a review of what you learned in your general physiology course, but it will now be expanded for use at the bedside. A number of useful reviews are included in the bibliography at the end of the chapter (1–4).

BASIC CONCEPTS

Hydrogen Ion Concentration and pH

The hydrogen ion concentration $[H^+]$ in aqueous solutions is traditionally expressed by the pH, which allegedly is an abbreviation for the *power of hydrogen*, and is a logarithmic function of the $[H^+]$; i.e.,

$$pH = \log (1/[H^+]) = - \log [H^+] \quad (31.1)$$

The physiological range of pH and corresponding $[H^+]$ is shown in Figure 31.1. The normal pH of plasma is 7.40, which corresponds to a $[H^+]$ of 40 nEq/L.

The relationships in Figure 31.1 show that changes in pH are not linearly related to changes in $[H^+]$. Note that the change in $[H^+]$ in the acidotic range (60 nEq/L) is about 2.5 times greater than in the alkalotic range (24 nEq/L), which means that changes in pH will have different implications for acid-base balance at different points along the pH spectrum.

Hydrogen Ion as Trace Element

Also evident in Figure 31.1 is that the concentration of H^+ is expressed in nanoequivalents per liter (nEq/L, or 10^{-9} Eq/L). One nanoequivalent is *one-millionth* of a milliequivalent (1 nEq = 1

× 10^{-6} mEq), so hydrogen ions are about a million times less dense than the principal ions in extracellular fluid (sodium and chloride), whose concentrations are expressed in mEq/L. This gives hydrogen ions the status of a trace element, but it is a very influential one, as shown by the fact that the normal pH range (7.36–7.44) corresponds to a change in $[H^+]$ of less than 10 nEq/L (!).

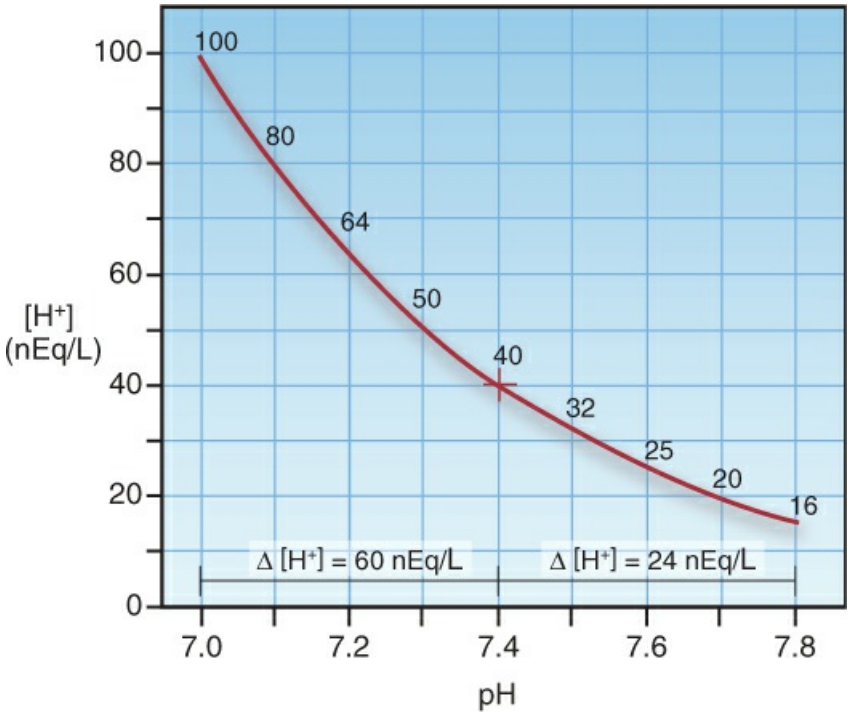

FIGURE 31.1 Graph describing the relationship between the extracellular (plasma) pH and hydrogen ion concentration. Note that the relationship is different in the acidotic and alkalotic ranges of plasma pH.

Classification of Acid-Base Disorders

According to traditional concepts of acid-base physiology, the $[H^+]$ in extracellular fluid is determined by the balance between the partial pressure of carbon dioxide (PCO_2) and the concentration of bicarbonate $[HCO_3]$ in the fluid. This relationship is expressed as follows (3):

$$[H^+] = 24 \times (PCO_2/HCO_3) \quad (31.2)$$

The PCO_2/HCO_3 ratio identifies all the primary acid-base disorders and compensatory responses, as shown in Table 31.1.

TABLE 31.1 Primary Acid-Base Disorders and Compensatory Responses

$\Delta [H^+] \sim \Delta PCO_2/\Delta HCO_3$		
Primary Disorder	**Primary Change**	**Compensatory Response†**
Respiratory Acidosis	↑ PCO_2	↑ HCO_3

Respiratory Alkalosis	↓ PCO_2	↓ HCO_3
Metabolic Acidosis	↓ HCO_3	↓ PCO_2
Metabolic Alkalosis	↑ HCO_3	↑ PCO_2

Primary Acid-Base Disorders

According to Equation 31.2, a change in either the PCO_2 or the HCO_3 will cause a change in the $[H^+]$ of extracellular fluid. When a change in PCO_2 initiates the change in $[H^+]$, the condition is called a *respiratory* acid-base disorder: an increase in PCO_2 is a *respiratory acidosis*, and a decrease in PCO_2 is a *respiratory alkalosis*. When a change in HCO_3 initiates the change in $[H^+]$, the condition is called a *metabolic* acid-base disorder: a decrease in HCO_3 is a *metabolic acidosis*, and an increase in HCO_3 is a *metabolic alkalosis*.

Compensatory Responses

Compensatory responses are designed to limit the change in $[H^+]$ produced by the primary acid-base disorder, and this is accomplished by changing the other component of the $PaCO_2/HCO_3$ ratio in the same direction as the component involved in the primary acid-base disturbance. For example, if the primary change is an increase in $PaCO_2$ (respiratory acidosis), the compensatory response will be an increase in HCO_3, which limits the final change in $[H^+]$. It is important to emphasize that *compensatory responses limit, but do not correct, the change in $[H^+]$ produced by the primary acid-base disorder*. The expected compensatory changes in each of the primary acid-base disorders are shown in Figure 31.2, and each of these is described next.

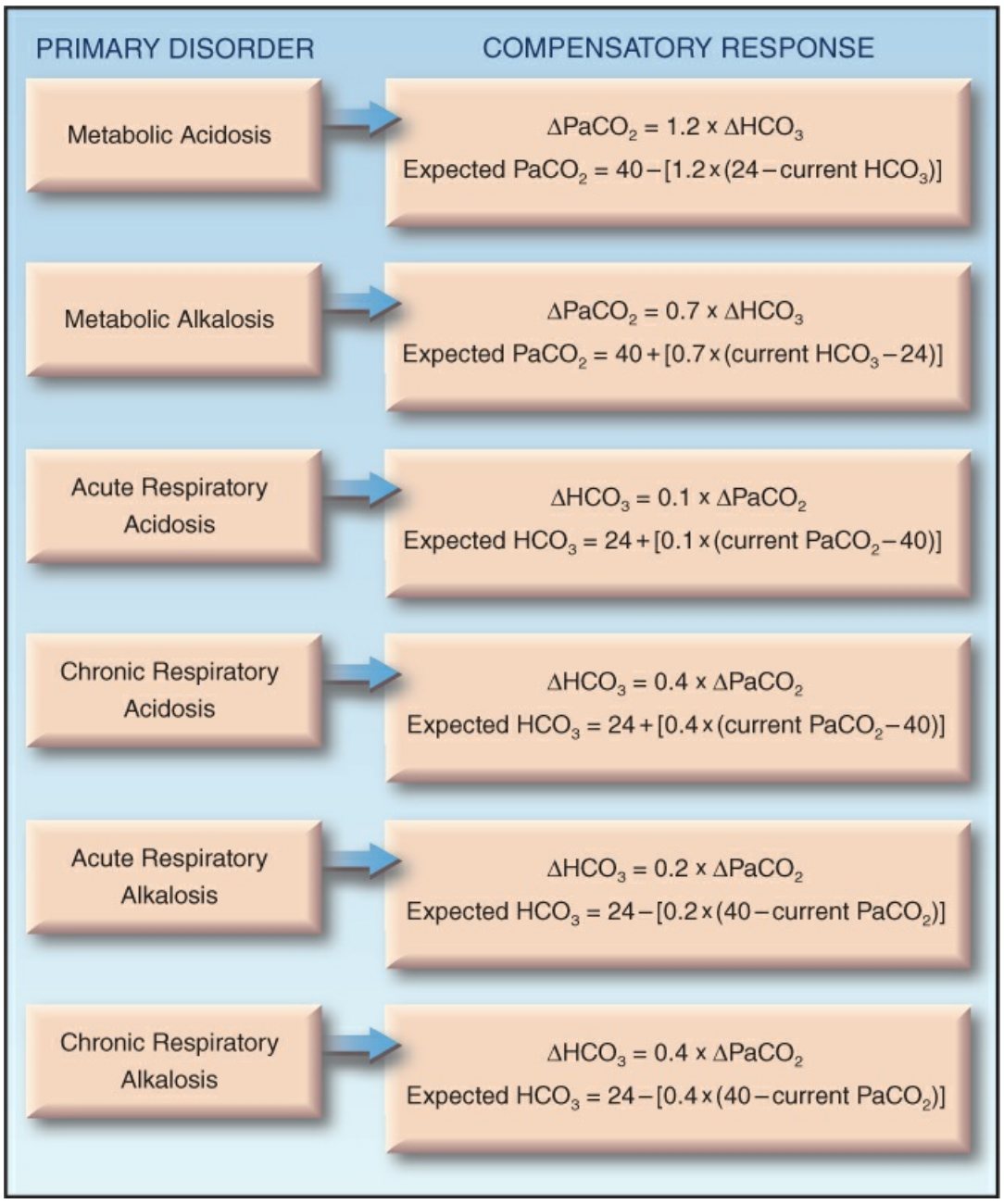

FIGURE 31.2 Predictive equations for evaluating secondary responses to primary acid-base disorders. All equations are from Reference 3.

Responses to Metabolic Acid-Base Disorders

The physiological response to a metabolic acid-base disorder is a change in minute ventilation, which is mediated by peripheral chemoreceptors in the carotid body located at the carotid bifurcation in the neck.

Metabolic Acidosis

The response to metabolic acidosis is an increase in minute ventilation (tidal volume and respiratory rate) and a subsequent decrease in $PaCO_2$. This response appears in 30–120 minutes,

and the magnitude of the response is defined by the equation below (3):

$$\Delta PaCO_2 = 1.2 \times \Delta HCO_3 \quad (31.3)$$

Using a normal $PaCO_2$ of 40 mm Hg and a normal HCO_3 of 24 mEq/L, the above equation can be rewritten as follows:

$$\text{Expected } PaCO_2 = 40 - [1.2 \times (24 - \text{current } HCO_3)] \quad (31.4)$$

EXAMPLE: For a metabolic acidosis with a plasma HCO_3 of 14 mEq/L:

. The ΔHCO_3 is 24 – 14 = 10 mEq/L

. The $\Delta PaCO_2$ is 1.2 × 10 = 12 mm Hg

. The expected $PaCO_2$ is 40 – 12 = 28 mm Hg.

a. If the measured $PaCO_2$ >28 mm Hg, there is a *secondary respiratory acidosis*.
b. If the measured $PaCO_2$ is <28 mm Hg, there is a *secondary respiratory alkalosis*.

Metabolic Alkalosis

The compensatory response to metabolic alkalosis is a decrease in minute ventilation, which increases the $PaCO_2$. This response is not as vigorous as the response to metabolic acidosis because the peripheral chemoreceptors are not very active under normal conditions, so they are more readily turned on than turned off. The expected change in $PaCO_2$ is defined by the equation below (3).

$$\Delta PaCO_2 = 0.7 \times \Delta HCO_3 \quad (31.5)$$

Using a normal $PaCO_2$ of 40 mm Hg and a normal HCO_3 of 24 mEq/L, the above equation can be rewritten as follows:

$$\text{Expected } PaCO_2 = 40 + [0.7 \times (\text{current } HCO_3 - 24)] \quad (31.6)$$

EXAMPLE: For a metabolic alkalosis with a plasma HCO_3 of 40 mEq/L:

. The ΔHCO_3 is 40 – 24 = 16 mEq/L

. The $\Delta PaCO_2$ is 0.7 × 16 = 11 mm Hg

. The expected $PaCO_2$ is 40 + 11 = 51 mm Hg.

a. If the measured $PaCO_2$ is >51 mm Hg, there is a *secondary respiratory acidosis*.
b. If the measured $PaCO_2$ is <51 mm Hg, there is a *secondary respiratory alkalosis*.

Responses to Respiratory Acid-Base Disorders

The compensatory response to primary changes in $PaCO_2$ occurs in the kidneys, where HCO_3

reabsorption in the proximal tubules changes in the same direction as the change in $PaCO_2$. This renal response is relatively slow, and can take 2 or 3 days to reach completion. Because of this delay, respiratory acid-base disorders are classified as acute or chronic (compensated).

Acute Respiratory Disorders

Acute changes in $PaCO_2$ have a minor effect on the plasma HCO_3, as described by the equations below (3).
For acute respiratory acidosis:

$$\Delta HCO_3 = 0.1 \times \Delta PaCO_2 \quad (31.7)$$

For acute respiratory alkalosis:

$$\Delta HCO_3 = 0.2 \times \Delta PaCO_2 \quad (31.8)$$

EXAMPLE: For an acute change in $PaCO_2$ of 20 mm Hg, the ΔHCO_3 is $0.1 \times 20 = 2$ mEq/L for an acute respiratory acidosis, and $0.2 \times 20 = 4$ mEq/L for an acute respiratory alkalosis. Neither of these changes would be recognized as significant.

Chronic Respiratory Disorders

The renal response to a respiratory acidosis (i.e., an increase in $PaCO_2$) is an increase in HCO_3 reabsorption in the proximal renal tubules, which raises the plasma HCO_3 concentration. The response to a respiratory alkalosis (i.e., a decrease in $PaCO_2$) is a decrease in renal HCO_3 reabsorption, which lowers the plasma HCO_3 concentration. The magnitude of this response is similar, regardless of the directional change in $PaCO_2$, so the equation below applies to both chronic respiratory acidosis and alkalosis.

$$\Delta HCO_3 = 0.4 \times \Delta PaCO_2 \quad (31.9)$$

Using a normal $PaCO_2$ of 40 mm Hg and a normal HCO_3 of 24 mEq/L, the above equation can be rewritten as follows:
For chronic respiratory acidosis:

$$\text{Expected } HCO_3 = 24 + [0.4 \times (\text{current } PaCO_2 - 40)] \quad (31.10)$$

For chronic respiratory alkalosis:

$$\text{Expected } HCO_3 = 24 - [0.4 \times (40 - \text{current } PaCO_2)] \quad (31.11)$$

EXAMPLE: For an increase in $PaCO_2$ to 60 mm Hg that persists for at least a few days:

. The $\Delta PaCO_2$ is $60 - 40 = 20$ mm Hg,

. The ΔHCO_3 is $0.4 \times 20 = 8$ mEq/L,

. The expected HCO_3 is 24 + 8 = 32 mEq/L.

STEPWISE APPROACH TO ACID BASE ANALYSIS

The following is a structured, rule-based approach to the diagnosis of primary, secondary, and mixed acid-base disorders using the relationships between the $[H^+]$, PCO_2, and HCO_3 just described. Several examples are included as instructional aids. The reference ranges for arterial pH, PCO_2 and HCO_3 are shown below.

pH = 7.36–7.44
PCO_2 = 36–44 mm Hg
HCO_3 = 22–26 mEq/L

Stage I: Identify Primary Acid-Base Disorders

The first stage of the approach uses the directional changes in the $PaCO_2$ and pH to identify the primary acid-base disorder.

Rule 1: If the $PaCO_2$ and pH are both abnormal, compare the directional change.

1a: If the $PaCO_2$ and pH change in the same direction, there is a primary metabolic acid-base disorder.

1b: If the $PaCO_2$ and pH change in opposite directions, there is a primary respiratory acid-base disorder.

EXAMPLE: Consider a case where the arterial pH = 7.23 and the $PaCO_2$ = 23 mm Hg. The pH and $PaCO_2$ are both reduced (indicating a primary metabolic disorder) and the pH is low (indicating an acidosis), so the diagnosis is a *primary metabolic acidosis*.

Rule 2: When the $PaCO_2$ is abnormal but the pH is normal, the condition can be called a *mixed* metabolic and respiratory disorder. The directional change in $PaCO_2$ identifies the type of respiratory disorder, and the metabolic disorder is then in the opposite direction. (This rule is based on the notion that compensatory responses do not correct the primary acid-base change.)

EXAMPLE: Consider a case where the arterial pH = 7.41 and the $PaCO_2$ = 60 mm Hg. Only the $PaCO_2$ is abnormal, so there is a mixed metabolic and respiratory disorder. The $PaCO_2$ is elevated, indicating a respiratory acidosis, so the metabolic disorder must be a metabolic alkalosis.

Stage II: Identify Secondary Acid-Base Disorders

The second stage uses the expected compensatory responses to identify any additional or secondary acid-base disorders. (*Note:* If a mixed acid-base disorder was identified in Stage I, this stage is not necessary).

Rule 3: For a primary metabolic disorder, determine the expected $PaCO_2$.

3a: If the measured $PaCO_2$ is higher than expected, there is a secondary respiratory acidosis.

3b: If the measured $PaCO_2$ is lower than expected, there is a secondary respiratory alkalosis.

EXAMPLE: Consider a case where the arterial pH = 7.28, $PaCO_2$ = 23 mm Hg, and the HCO_3 = 14 mEq/L. The pH and $PaCO_2$ change in the same direction, indicating a primary metabolic disorder, and the pH is below normal, indicating an acidosis, so the disorder is a primary metabolic acidosis. Using Equations 31.3 and 31.4:

. The $\Delta PaCO_2$ is $1.2 \times (24 - 14) = 12$ mm Hg,

. The expected $PaCO_2$ is then $40 - 12 = 28$ mm Hg.

The measured $PaCO_2$ (23 mm Hg) is lower than the expected $PaCO_2$, so there is an additional respiratory alkalosis. Therefore, this condition is a *primary metabolic acidosis with a secondary respiratory alkalosis*.

Rule 4: For a primary respiratory disorder, determine the expected HCO_3 for both acute and chronic (compensated) conditions. If the measured HCO_3 is between the expected HCO_3 for the acute and chronic conditions, it is a *partially compensated respiratory disorder*.

4a: For a primary respiratory acidosis,

1. If the measured HCO_3 is less than the expected HCO_3 for the acute condition, there is a secondary metabolic acidosis.
2. If the measured HCO_3 is higher than expected for the chronic condition, there is a secondary metabolic alkalosis.

4b: For a primary respiratory alkalosis:

1. If the HCO_3 is higher than expected for the acute condition, there is a secondary metabolic alkalosis.
2. If the HCO_3 is lower than expected for the chronic condition, there is a secondary metabolic acidosis.

EXAMPLE: Consider a case where the $PaCO_2$ = 26 mm Hg, the pH = 7.50, and the HCO_3 = 14 mEq/L. The $PaCO_2$ and pH change in opposite directions, indicating a primary respiratory disorder, and the pH is alkaline, so the disorder is a primary respiratory alkalosis. Using Equations 31.8 and 31.9:

. The ΔPCO_2 is $40 - 26 = 14$ mm Hg

. The acute ΔHCO_3 should be $0.2 \times 14 = 3$ mEq/L

. The chronic ΔHCO_3 should be $0.4 \times 14 = 6$ mEq/L

. The expected HCO_3 range is then 18–21 mEq/L.

The measured HCO_3 is 14 mEq/L, which is lower than the expected range of HCO_3 values, so this condition is a *primary respiratory alkalosis with a secondary metabolic acidosis*.

Stage III: Use The "Gaps" to Evaluate a Metabolic Acidosis

The final stage of this approach is for patients with a metabolic acidosis, where the use of measurements called "gaps" can help to uncover the underlying cause of the acidosis. These are described in the next section.

THE GAPS

There are numerous potential sources of a metabolic acidosis in critically ill patients, and the measurements described in this section are designed to help narrow the list of suspects.

The Anion Gap

The anion gap is a rough estimate of the relative abundance of unmeasured anions, and is used to determine if a metabolic acidosis is due to an accumulation of non-volatile acids (e.g., lactic acid) or a primary loss of bicarbonate (e.g., diarrhea) (5,6).

Determinants

To achieve electrochemical balance, the concentration of negatively charged anions must equal the concentration of positively charged cations. This electrochemical balance is expressed in the equation shown below using the most abundant electrolytes in the extracellular fluid, along with the unmeasured cations (UC) and unmeasured anions (UA).

$$(Na) + UC = (CL + HCO_3) + UA \tag{31.12}$$

Rearranging the terms in this equation yields the following relationships:

$$(Na) - (CL + HCO_3) = UA - UC \tag{31.13}$$

The difference (UA − UC) is a measure of the relative abundance of unmeasured anions in extracellular fluid, and is called the *anion gap* (AG). The electrolytes in Equation 31.13 are all routinely obtained in hospitalized patients, and this provides a simple and readily available method for calculating the AG.

$$AG = (Na) - (CL + HCO_3) \tag{31.14}$$

REFERENCE RANGE: The reference range for the AG is typically stated as 8–12 mEq/L (5,6), but electrolyte measurements can differ slightly in different clinical laboratories, so each laboratory should publish their reference range for the AG.

Influence of Albumin

The unmeasured anions and cations that normally contribute to the anion gap are shown in Table 31.2. Note that albumin is the principal unmeasured anion, and thus is the principal determinant

of the anion gap. Albumin is a weak acid that contributes about 2.5 mEq per gram to the anion gap (5,7). A low albumin level in plasma will lower the AG, and this could mask the presence of an unmeasured anion (e.g., lactate) that is contributing to a metabolic acidosis. Since hypoalbuminemia is present in as many as 90% of ICU patients, the following formula for the "corrected AG" (AGc) is recommended (7):

$$\text{Corrected AG} = \text{AG} + [2.5 \times (4.5 - \text{albumin})] \tag{31.15}$$

where 4.5 represents the normal concentration of albumin in plasma (in g/dL).

EXAMPLE: For a patient with a normal AG of 10 mEq/L and a plasma albumin of 2 g/dL, the corrected AG is 10 + (2.5 × 2.5) = 16 mEq/L, so the albumin conversion turned a normal AG into an elevated AG, which has significant implications for determining the cause of a metabolic acidosis, as explained next.

TABLE 31.2 Determinants of the Anion Gap

Unmeasured Anions	Unmeasured Cations
Albumin (15 mEq/L)	Calcium (5 mEq/L)
Organic Acids (5 mEq/L)	Potassium (4.5 mEq/L)
Phosphate (2 mEq/L)	
Sulfate (1 mEq/L)	Magnesium (1.5 mEq/L)
Total UA: (23 mEq/L)	Total UC: (11 mEq/L)

Anion Gap = UA – UC = 12 mEq/L

Using the Anion Gap

The AG can be used to identify the underlying mechanism of a metabolic acidosis, which then helps to identify the underlying clinical condition. An elevated AG occurs when there is an accumulation of fixed or non-volatile acids (e.g., lactic acid), while a normal AG occurs when there is a primary loss of bicarbonate (e.g., diarrhea) (7) . Table 31.3 shows the causes of metabolic acidosis grouped according to the AG.

TABLE 31.3 Causes of Metabolic Acidosis Based on the Anion Gap

High Anion Gap	Normal Anion Gap
L-Lactic Acid	Diarrhea
D-Lactic acid	Isotonic saline infusion
Ketoacids	Early renal insufficiency
Ethylene Glycol (Oxalic Acid)	Renal tubular acidosis
Methanol (Formic Acid)	Acetazolamide

Pyroglutamic Acid†	Ureteroenterostomy
Salicylate Toxicity	
Advanced Renal Failure	

†Also known as 5-oxoproline, and associated with chronic acetaminophen ingestion.

HIGH ANION GAP: Common causes of high AG metabolic acidosis include lactic acidosis, diabetic ketoacidosis, and advanced renal failure (where there is loss of H^+ secretion in the distal tubules of the kidneys). Also included are toxic ingestions of methanol (which produces formic acid), ethylene glycol (which produces oxalic acid), and salicylates (which produce salicylic acid) (5). Two often unrecognized causes of a high gap metabolic acidosis that deserve mention are summarized as follows.

. Lactic acid has two optical isomers (named *dextro* and *levo* by the direction of light reflection), and most clinical laboratories measure only the levo form (L-lactic acid). However, some gut microbes can produce D-lactic acid from carbohydrate metabolism, and a high anion gap metabolic acidosis from elevated D-lactate levels has been reported in patients with short bowel syndrome (8). These patients often develop neurologic manifestations, such as confusion, agitation, ataxia, and nystagmus (9). Although this is an uncommon condition, it will be missed unless a formal request for a D-lactate measurement is submitted to the hospital laboratory. Of interest, D-lactic acid may also contribute to the metabolic acidosis produced by propylene glycol toxicity (5).

. Another often unrecognized cause of a high anion gap metabolic acidosis is 5-oxoproline (also known as pyroglutamic acid), which is associated with chronic ingestion of acetaminophen (10). 5-oxoproline is involved in glutathione synthesis, but why it accumulates in some cases of chronic acetaminophen ingestion is unclear. Serum levels of acetaminophen are usually in the therapeutic range (10). Although this condition is considered rare, the actual incidence is unknown because 5-oxoproline levels are not routinely available.

NORMAL ANION GAP: In the ICU, most cases of normal AG metabolic acidosis are the result of isotonic saline infusions (see Chapter 10), diarrhea, or early renal insufficiency (where there is a defect of bicarbonate reabsorption in the proximal tubules). This type of acidosis is characterized by an increase in chloride concentration (to electrically balance the decrease in HCO_3); hence the term *hyperchloremic metabolic acidosis* is used for normal AG metabolic acidoses. (In high AG metabolic acidoses, the remaining anions from the dissociated acids balance the loss of HCO_3, so there is no associated hyperchloremia.)

The Delta Gap

The delta gap is the ratio of the increase in the anion gap to the decrease in plasma HCO_3, and is described by the following equation:

$$\text{AG Excess}/HCO_3\ \text{Deficit} = (\text{AG} - 12)/(24 - HCO_3) \qquad (31.16)$$

where 12 is the normal anion gap (in mEq/L) and 24 is the normal plasma HCO_3 (in mEq/L). This ratio is sometimes called the *gap-gap* because it involves two gaps (the AG excess and the HCO_3 deficit). The delta gap can be useful in identifying mixed acid-base disorders (11), as

described next.

Mixed Metabolic Acidoses

In metabolic acidoses caused by non-volatile acids (high AG metabolic acidosis), the increase in the anion gap should be equivalent to the decrease in plasma HCO_3: i.e., the delta gap should be 1.0. (In the real world, differences in distribution and clearance rate create slightly different delta gaps for different acids). However, if there is a second source of acidosis that is a normal AG (hyperchloremic) acidosis, the decrease in HCO_3 is greater than the increase in AG, and the delta gap ratio falls below 1.0. Therefore, *in the presence of a high AG metabolic acidosis, a delta gap <1 indicates the co-existence of a normal AG (hyperchloremic) metabolic acidosis* (12).

DIABETIC KETOACIDOSIS: Diabetic ketoacidosis (DKA) is a high AG metabolic acidosis with delta gap = 1. However, during the management of DKA, the aggressive infusion of isotonic saline creates a normal AG metabolic acidosis. In this situation, the serum bicarbonate decreases relative to the anion gap, resulting in a delta gap <1 (12). Therefore, monitoring the plasma HCO_3 alone will create a false impression that the DKA is not resolving, while the delta gap provides an accurate assessment of the changing acid-base status.

Metabolic Acidosis and Alkalosis

When alkali is added in the presence of a high AG acidosis, the decrease in serum bicarbonate is less than the increase in AG, and the delta gap is >1. Therefore, *in the presence of a high AG metabolic acidosis, a delta-gap >1 indicates the co-existence of a metabolic alkalosis* (4). This is an important consideration because metabolic alkalosis is common in ICU patients (e.g., from the frequent use of diuretics).

Osmolal Gap

The osmolality of plasma can be calculated using the concentrations of the major solutes in extracellular fluid (i.e., sodium, chloride, glucose, and urea): i.e.,

$$\text{Posm} = 2 \times [\text{Na}^+] + \frac{\text{Glucose}}{18} + \frac{\text{BUN}}{2.8} \tag{31.17}$$

where Posm is the plasma osmolality in mosm/kg H_2O, $[Na^+]$ is the plasma sodium concentration in mEq/L, glucose and BUN are the glucose and urea concentrations in plasma in mg/dL, and the factors 18 and 2.8 are the molecular weights of glucose and urea divided by 10, respectively, to express their concentrations in mosm/kg H_2O. The $[Na^+]$ is doubled to include the osmotic activity of chloride.

Using normal plasma concentrations of Na^+ (140 mEq/L), glucose (90 mg/dL), and BUN (14 mg/dL), in Equation 31.17 yields a calculated plasma osmolality of 290 mosm/kg H_2O. The plasma osmolality can also be measured, and the difference between the measured and calculated plasma osmolality is normally <10 mosm/kg H_2O (13). This difference is known as the *osmolal gap*.

Detecting Hidden Solutes

When a solute other than those in Equation 31.17 is added to the extracellular fluid, the measured plasma osmolality will increase, while the calculated osmolality will be unaffected; i.e., the osmolal gap will increase. Thus, an increased osmolal gap can be used to detect an occult toxin (14), and in cases of high AG metabolic acidosis where the common offenders (lactic acid, ketoacids) are not responsible, an elevated osmolal gap can indicate the presence of an occult, unmeasured acid (e.g., D-lactic acid, oxalic acid, formic acid, salicylates, pyroglutamic acid).

A FINAL WORD

Distrusting the Simplicity

For more than 100 years, the evaluation of acid-base balance has been based on a single reaction sequence (shown below), and a single determinant of the plasma pH (i.e., the $PaCO_2/HCO_3$ ratio).

$$CO_2 + H_2O \Leftrightarrow H_2CO_3 \Leftrightarrow H^+ + HCO_3 \quad (31.18)$$

This approach is appealing because of its simplicity, but as Lord Whitehead advises in the introductory quote, simplification can have drawbacks. The following are some major drawbacks with the traditional acid-base paradigm.

. The use of the $PaCO_2$-HCO_3 relationship to identify acid-base disorders is flawed because the CO_2 in plasma is present primarily as HCO_3, so it is difficult to establish an independent identity for HCO_3.

. Bicarbonate does not act as a buffer in the physiological pH range (which is demonstrated in the next chapter). In fact, the plasma $[H^+]$ is a function of the anionic charge equivalence of the plasma proteins, and is not directly related to the plasma HCO_3 (15,16).

There is an alternative (and more valid) physicochemical view of acid-base balance, which was introduced by Peter Stewart (a Canadian physiologist), and the bibliography includes a textbook and original paper by Stewart for any who are interested (15,16).

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Chapter 32

Lactic Acidosis and Ketoacidosis

Fundamental progress has to do with the reinterpretation of basic ideas.

Alfred North Whitehead (*a*)

This chapter focuses on the two most prominent acid-base disorders you will encounter in the ICU: lactic acidosis and ketoacidosis. However, as you will learn, the problem with these disorders has little to do with the acid-base disturbances they promote. Also covered in this chapter is alkali therapy with bicarbonate, and the reasons to avoid it.

LACTIC ACIDOSIS

Lactate is a three-carbon anion that is formed by the chemical reduction of pyruvate in the cytoplasm, in a reaction catalyzed by the lactate dehydrogenase (LDH) enzyme. About 1,500 mmoles of lactate are produced daily under aerobic conditions (1,2), and the principal sites of production are skeletal muscle (25%), skin (25%), red blood cells (20%), brain (20%), and intestine (10%). Activated neutrophils are an additional source of lactate in inflammatory conditions (3). The concentration of lactate in plasma is usually ≤2 mmol/L, with a lactate:pyruvate ratio of 10:1 (1,2). Lactate is cleared from plasma by the liver (60%), kidneys (30%) and heart (10%).

The Evolving Lactate Paradigm

The traditional teaching has been that anaerobic conditions are the principle source of increased lactate production. However, the description of lactate metabolism in Chapter 9 introduces the following notions:

. Lactate production is NOT driven by anaerobic metabolism (see Table 9.5).

. Lactate serves as an oxidative fuel in conditions of metabolic stress, with a caloric yield that is equivalent to glucose (see Table 9.6).

During conditions of metabolic stress, when glucose availability is limited, lactate can

provide 60% of the energy needs of the myocardium (4), and 30% of the energy needs of the brain (5). During exercise, about three-quarters of the lactate produced is used as an oxidative fuel, and in exercising muscle, there is an intercellular lactate shuttle that transfers lactate from white “glycolytic” muscle fibers to red “oxidative” muscle fibers (6). (Please review the material in Chapter 9 for a more detailed description of these issues.) Another misconception about lactate production that has been known for years, but is rarely mentioned, is described next.

Lactate is Not an Acid

The traditional teaching has been that lactic acid is the end-product of glucose metabolism in the cytoplasm (glycolysis), but there are a number of problems with this scenario, as indicated by the numbers in Figure 32.1 (7,8).

. The end-product of glycolysis is the lactate anion, which is not an acid.

. The chemical reaction that produces lactate actually *consumes* hydrogen ions, which should have the opposite effect to the production of an acid.

. The hydrogen ions associated with lactate production are attributed to the hydrolysis of the 2 ATP molecules formed during glycolysis (8), but how this influences extracellular pH is unclear.

Each of these points is contrary to the traditional explanation for lactic acidosis, and an alternative explanation is warranted. The fact that hyperlactatemia can exist without an associated acidosis (9) is further evidence of the incomplete understanding of the relationship between lactate production and acidosis.

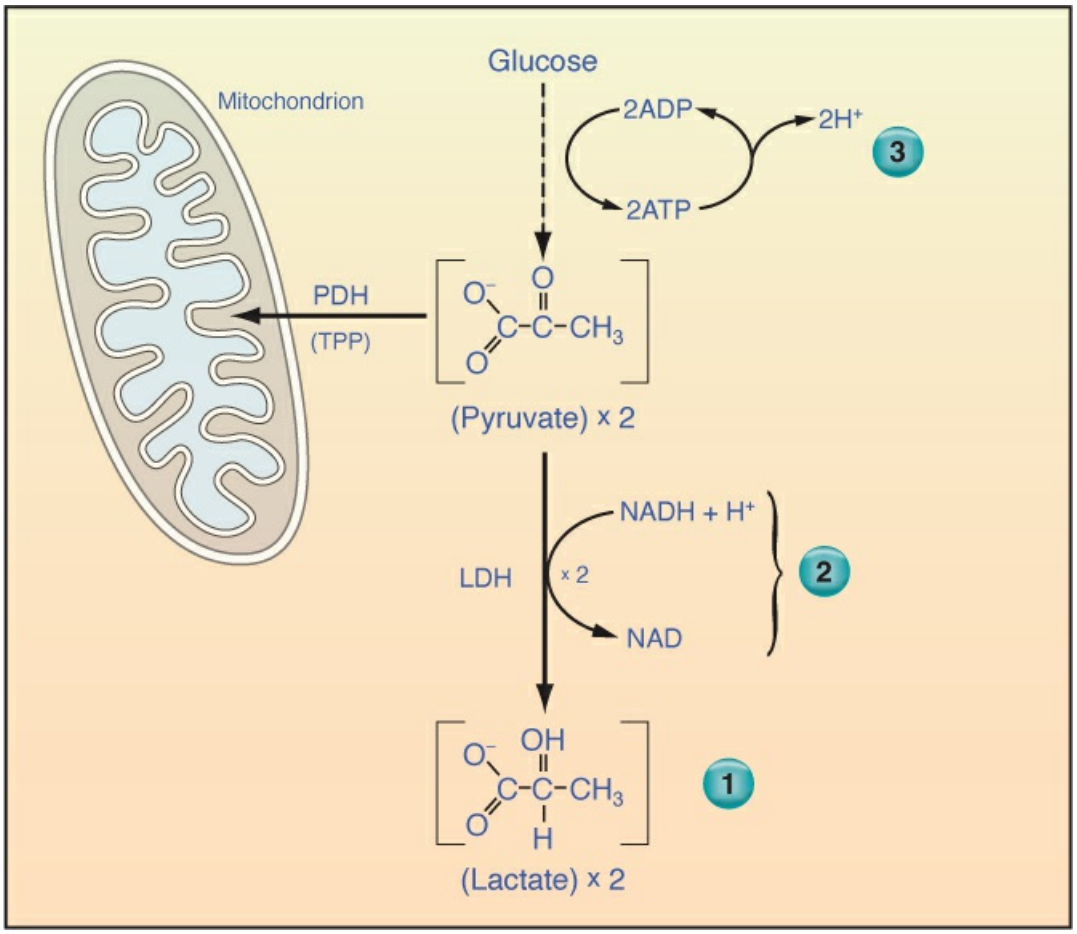

FIGURE 32.1 Problems with the association between lactate production and acidosis. See text for explanation. PDH = pyruvate dehydrogenase, LDH = lactate dehydrogenase, TPP = thiamine pyrophosphate.

Prognostic Value

Regardless of its origins or function, plasma lactate levels have prognostic significance in critically ill patients: i.e.,

. The initial lactate level has a direct relationship with mortality rates, as shown in the left-hand graph in Figure 9.4 (10,11).

. The time required for lactate levels to return to normal (lactate clearance) has greater predictive value than the initial lactate level. Normalization of lactate levels within 24 hours is associated with the lowest mortality rates (see the graph on the right in Figure 9.4) (11).

Causes of Hyperlactatemia

There are numerous causes of elevated plasma lactate levels, and the major ones are listed in Table 32.1.

TABLE 32.1 The Myriad Causes of Hyperlactatemia

Conditions	Drugs and Toxins

Asthma (acute) Circulatory Shock Compartment Syndromes DKA Liver Failure Leukemia/Lymphoma Mesenteric Ischemia Pheochromocytoma Seizures Sepsis Strenuous Exercise Thiamine Deficiency	Drugs: Antiretrovirals Epinephrine Linezolid Metformin Propofol Toxins: Carbon Monoxide Cyanide Propylene Glycol

Clinical Shock Syndromes

The most notable, and most feared sources of hyperlactatemia are the *clinical shock syndromes;* i.e., hypovolemic, cardiogenic, and septic shock.

SEPTIC SHOCK: Sepsis or septic shock may be the most common cause of lactic acidosis in critically ill patients. The source of elevated lactate levels is a combination of increased production of pyruvate (12) and a defect in O_2 utilization in mitochondria (called c*ytopathic hypoxia*) (13), which may be caused by inhibition of the pyruvate dehydrogenase enzyme responsible for pyruvate entry into mitochondria (see Figure 32.1) (14,15). Tissue oxygenation is not impaired, and can actually be increased (see Figure 17.3).

Systemic Inflammatory Response Syndrome

Systemic inflammation (fever, leukocytosis, etc.) can be accompanied by mild elevations of blood lactate (2 to 5 mEq/L) with a normal lactate:pyruvate ratio and a normal plasma pH. This condition is called *stress hyperlactatemia*, and is the result of an increase in the production of pyruvate without a defect in tissue oxygenation or oxygen utilization (13). The lactate elevation in severe sepsis and septic shock is usually associated with increased lactate:pyruvate ratios and a decrease in plasma pH.

Thiamine Deficiency

The manifestations of thiamine deficiency include high-output heart failure (wet beriberi), Wernicke's encephalopathy, peripheral neuropathy (dry beriberi), and lactic acidosis. The lactic acidosis can be severe (16), and is caused by a deficiency in thiamine pyrophosphate, which serves as a co-factor for pyruvate dehydrogenase (see Figure 32.1). Thiamine deficiency may be more common than suspected in critically ill patients, and should be considered in all cases of unexplained lactic acidosis. (See Chapter 48 for a more detailed description of thiamine deficiency.)

Pharmaceutical Agents

More than 300 medications have been implicated as a cause of elevated plasma lactate levels (17), and the common ones are listed in the right-hand column of Table 32.1.

EPINEPHRINE: Hyperlactatemia is a consequence of high-dose therapy with epinephrine and albuterol (17). Both act by increasing the rate of glycolysis, and produce hyperlactatemia that is aerobic in origin. The albuterol effect may explain reports of lactic acidosis in cases of acute asthma.

METFORMIN: Metformin is an oral hypoglycemic agent that can precipitate lactic acidosis during therapeutic dosing. The mechanism for the lactic acidosis is unclear, but it occurs primarily in patients with renal insufficiency, and has a mortality rate of 17–30% (18,19). Plasma metformin levels are not routinely available, and the diagnosis is based on excluding other causes of lactic acidosis. The preferred treatment is hemodialysis rather than alkali therapy (18,19).

ANTIRETROVIRAL AGENTS: Hyperlactatemia is reported in 8–18% of patients receiving antiretroviral therapy for HIV infection (20). The responsible drugs are the nucleoside analogues (e.g., didanosine, stavudine), and the presumed mechanism is inhibition of mitochondrial DNA polymerase (21). In most cases, the hyperlactatemia is mild and not associated with acidemia, but lactate levels above 10 mmol/L have a reported mortality rate of 33–57% (21).

LINEZOLID: Lactic acidosis is an uncommon but life-threatening complication of therapy with linezolid. The mechanism is unknown, and the reported mortality rate is 25% (22). It is more common in men, and can appear at any time during linezolid therapy.

Non-Pharmaceutical Toxidromes

Lactic acidosis can be the result of intoxications with cyanide, carbon monoxide, and propylene glycol. Cyanide and carbon monoxide intoxication are described in Chapter 53, and the following is a brief description of propylene glycol toxicity.

PROPYLENE GLYCOL: Propylene glycol is used as a solvent to increase the water solubility of some intravenous drug preparations, most notably lorazepam, diazepam, esmolol, nitroglycerin, and phenytoin. About 55–75% of propylene glycol is metabolized by the liver and the primary metabolite is lactate (both levo and dextro isomers) (23). *Propylene glycol toxicity* (i.e., agitation, coma, seizures, hypotension, and lactic acidosis) *has been reported in 19% to 66%* of *patients receiving high-dose intravenous lorazepam for more than 2 days* (24,25). If suspected, the drug infusion should be stopped and another sedative agent (other than diazepam) should be selected. An assay for propylene glycol in blood is available, but the acceptable range has not been determined.

Lactic Alkalosis

Severe alkalosis (respiratory or metabolic) can raise blood lactate levels as a result of increased activity of pH-dependent enzymes in the glycolytic pathway (9,26). When liver function is normal, the liver clears the extra lactate generated during alkalosis, and *lactic alkalosis* becomes evident only when the blood pH is 7.6 or higher. However, in patients with impaired liver function, hyperlactatemia can be seen with less severe degrees of alkalemia.

Other Sources

Other possible causes of hyperlactatemia in ICU patients include *generalized seizures* (from

hypermetabolism) (27), *hepatic insufficiency* (from reduced lactate clearance) (28), *acute asthma* (from enhanced lactate production by albuterol or respiratory muscles) (29), and *hematologic malignancies* (30). Hyperlactatemia that accompanies generalized seizures can be severe (with plasma lactate levels up to 15 mmol/L) but is transient (27).

Diagnostic Considerations

The normal lactate concentration in blood is ≤2 mmol/L, but increases in lactate concentration do not have prognostic value until they reach 4 mmol/L (1). Measurements can be obtained on arterial or venous blood samples. If immediate measurements are unavailable, the blood should be placed on ice to retard lactate production by red blood cells.

The anion gap (described in Chapter 31) should be elevated in lactic acidosis, but there are numerous reports of a normal anion gap in patients with lactic acidosis (31). As a result, *the anion gap should not be used as a screening test for lactic acidosis*.

D-Lactic Acidosis

The lactate produced by mammalian tissues is a levo isomer (l-lactate), whereas a dextro isomer of lactate (d-lactate) is produced by certain strains of bacteria that can populate the bowel (32). D-lactate generated by bacterial fermentation in the bowel can gain access to the systemic circulation and produce a metabolic acidosis, often combined with a metabolic encephalopathy (33). Most cases of d-lactic acidosis have been reported after extensive small bowel resection or after jejunoileal bypass for morbid obesity (32–34).

DIAGNOSIS: D-lactic acidosis can produce an elevated anion gap, but the standard laboratory assay for blood lactate measures only l-lactate. If d-lactic acidosis is suspected, you must specifically request a d-lactate assay.

ALKALI THERAPY

The primary goal of therapy in lactic acidosis is to correct the underlying metabolic abnormality. Alkali therapy aimed at correcting the pH is of questionable value (35). The following is a brief summary of the pertinent issues regarding alkali therapy for lactic acidosis.

Acidosis is Not Harmful

The principal fear from acidosis is the risk of impaired myocardial contractility (36), but this observation comes from isolated heart preparations. *In the intact organism, acidemia is accompanied by an increase in cardiac output* (37), because acidosis stimulates catecholamine release from the adrenal glands.

Protective Role?

Acidosis may have a protective role in life-threatening conditions, since extracellular acidosis has been shown to protect energy depleted cells from cell death (38). The protective role of acidosis is the basis for *pickling*, which is the preservation of food in vinegar (acetic acid), which typically has a pH of 4.0.

Bicarbonate is Not an Effective Buffer

Sodium bicarbonate has limited success in raising the plasma pH in cases of lactic acidosis (39). This can be explained by the titration curve for the carbonic acid bicarbonate buffer system, which is shown in Figure 32.2. The HCO_3 buffer pool is generated by the dissociation of carbonic acid (H_2CO_3):

$$CO_2 + H_2O \Leftrightarrow H_2CO_3 \Leftrightarrow H^+ + HCO_3^- \quad (32.1)$$

The dissociation constant (pK) for carbonic acid (i.e., the pH at which the acid is 50% dissociated) is 6.1, as indicated on the titration curve. Buffers are effective within 1 pH unit on either side of the pK (40), so the effective range of the bicarbonate buffer system is an extracellular pH between 5.1 and 7.1 pH units (indicated by the shaded area on the titration curve). Therefore, *bicarbonate is not an effective buffer in the usual pH range of extracellular fluid*. Bicarbonate is not really a buffer; rather, it is the end-product of CO_2 transport in blood (i.e., the CO_2 added to venous blood enters red blood cells (RBCs), where the carbonic anhydrase enzyme promotes the conversion of CO_2 to H^+ and HCO_3^-. The H^+ is buffered by hemoglobin, and the HCO_3^- is transported out of the RBCs and into plasma in exchange for chloride ions).

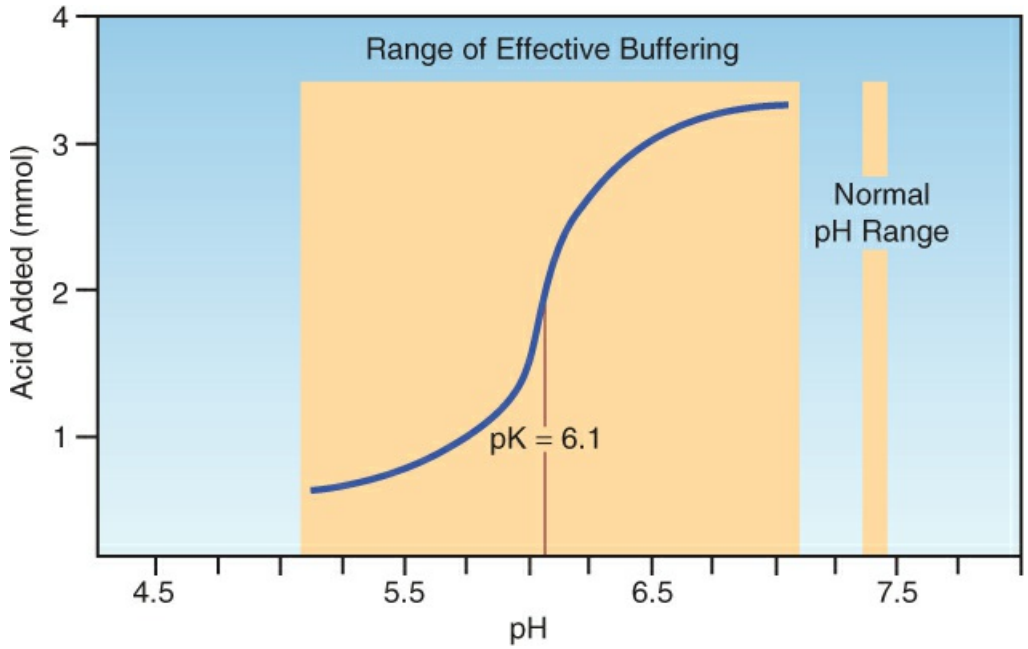

FIGURE 32.2 The titration curve for the carbonic acid-bicarbonate buffer system. The large, shaded area indicates the effective pH range for the bicarbonate buffer system, which does not coincide with the physiological pH range of extracellular fluid. Adapted from Reference 40.

Bicarbonate is Counterproductive

Bicarbonate infusions generate CO_2, which enters cells and cerebrospinal fluid and actually *lowers the intracellular pH* and cerebrospinal fluid pH (41,42). In fact, considering that *the PCO_2 is 200 mm Hg in standard bicarbonate solutions*, bicarbonate is really a CO_2 load that

must be removed by the lungs.

Bicarbonate infusions can also increase blood lactate levels (42). This effect is attributed to alkalosis-induced increase in lactate production, which is far from desirable for a proposed therapy of lactic acidosis.

Recommendation

Despite the wealth of evidence showing no benefits, and potential harm, from bicarbonate therapy, most (but not all) experts recommend bicarbonate therapy for severe lactic acidosis, when the pH is ≤7.1 and/or the plasma HCO_3 is ≤5 mEq/L) (43,44). It seems more reasonable to include only patients who are hemodynamically unstable (e.g., on vasopressors).

Bicarbonate therapy is probably most helpful in patients with lactic acidosis and renal insufficiency (where part of the problem is loss of HCO_3). The HCO_3 deficit can be estimated as follows (42):

$$HCO_3 \text{ deficit (mEq)} = 0.6 \times \text{wt (kg)} \times (15 - \text{measured } HCO_3) \quad (32.2)$$

(where 15 mEq/L is the desired plasma HCO_3). Half of this deficit can be replaced, and if this results hemodynamic improvement, bicarbonate therapy can be continued to maintain the plasma HCO_3 at 15 mEq/L. If no improvement or further deterioration occurs, further bicarbonate administration is not warranted. The composition of commonly used bicarbonate solutions is shown in Table 32.2.

TABLE 32.2 Composition of Sodium Bicarbonate Solutions

	7.5% $NaHCO_3$	8.4% $NaHCO_3$
Unit Volume (ampule)	50 mL	50 mL
HCO_3 Concentration	0.9 mEq/mL	1 mEq/mL
HCO_3 Content	45 mEq/ampule	50 mEq/ampule
Osmolarity	1,790 mosm/L	2,000 mosm/L

Sodium bicarbonate is also available as 4.2% and 5% solutions, but these are rarely used.

EXAMPLE: For a 70 kg adult with a pH of 7.0 and a plasma HCO_3 of 5 mEq/L, the HCO_3 deficit is $0.6 \times 70 \times 10 = 420$ mEq. One ampule (50 mL) of 8.4% $NaHCO_3$ contains 50 mEq HCO_3 (1 mEq/mL), so 4 amps of 8.4% $NaHCO_3$ (200 mEq HCO_3) would replace about half of the HCO_3 deficit. Since 8.4% $NaHCO_3$ is very hypertonic (2,000 mosm/L), it should be mixed with D_5W and infused slowly (over hours). The ionized calcium should be monitored during bicarbonate infusions, as raising the pH will decrease the ionized calcium, and this can lead to hemodynamic instability. In ventilator-dependent patients, an increase in minute ventilation will also be needed to eliminate the extra CO_2 produced by the bicarbonate infusion.

KETOACIDS

Ketogenesis

When carbohydrates are not available for metabolic energy production, there is a breakdown of triglycerides in adipose tissue to generate fatty acids, which are transported to the liver and metabolized to form three ketones; i.e., acetoacetate, β-hydroxybutyrate, and acetone. This is illustrated in Figure 32.3. These ketones are released from the liver and can be used as oxidative fuels by vital organs such as the heart and central nervous system. The oxidative metabolism of ketones yields 4 kcal/g, which is slightly in excess of the energy yield from the oxidative metabolism of glucose (3.7 kcal/g).

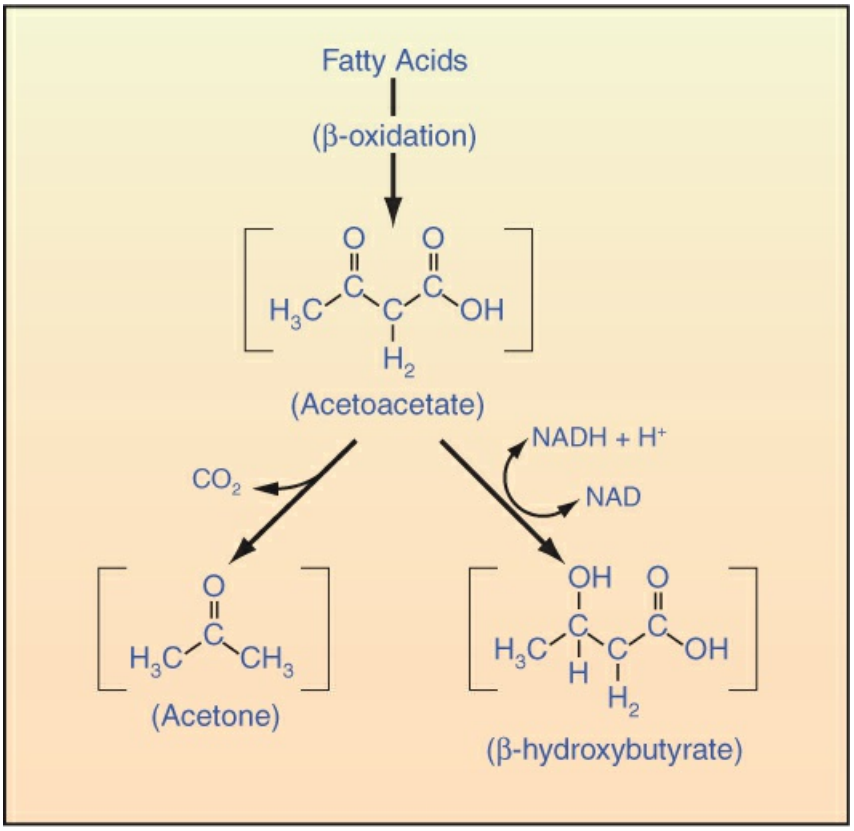

FIGURE 32.3 Ketogenesis in the liver, which occurs in response to diminished availability of glucose. Acetone is a ketone, but is not a ketoacid.

Ketoacids in Blood

The normal concentration of ketones in the blood is negligible (0.1 mmol/L), but blood ketone levels increase tenfold (to 1 mmol/L) after just 3 days of starvation. Acetone is not a ketoacid, but is responsible for the "fruity" odor of breath in patients with ketoacidosis. Acetoacetate (AcAc) and β-hydroxybutyrate (β-OHB) are strong acids, and produce a decrease in plasma pH when their plasma concentrations reach 3 mmol/L (45). The balance of AcAc and β-OHB in blood is determined by the following redox reaction (as shown in Figure 32.3):

$$\text{AcAc} + \text{NADH} + \text{H}^+ \leftrightarrow \beta\text{-OHB} + \text{NAD} \qquad (32.3)$$

The balance of this reaction normally favors the formation of β-OHB: i.e., in conditions of enhanced ketone production, the β-OHB:AcAc ratio ranges from 3:1 in diabetic ketoacidosis, to as high as 8:1 in alcoholic ketoacidosis. The concentration of ketoacids in the blood in diabetic and alcoholic ketoacidosis is shown in Figure 32.4. Note the preponderance of β-OHB in both conditions.

The Nitroprusside Reaction

The nitroprusside reaction is a colorimetric method for detecting AcAc and acetone in blood and urine. The test can be performed with tablets (Acetest) or reagent strips (Ketostix, Labstix, Multistix). A detectable reaction requires a minimum AcAc concentration of 3 mmol/L. Because *this reaction does not detect the predominant ketoacid, β-hydroxybutyrate* (45), it is an insensitive method for monitoring the severity of ketoacidosis. This is illustrated in Figure 32.4. In alcoholic ketoacidosis, the total concentration of ketoacids in blood is 13 mmol/L, which represents more than a hundredfold increase over the normal concentration of blood ketones, yet the nitroprusside reaction will be negative because the AcAc concentration is below 3 mmol/L.

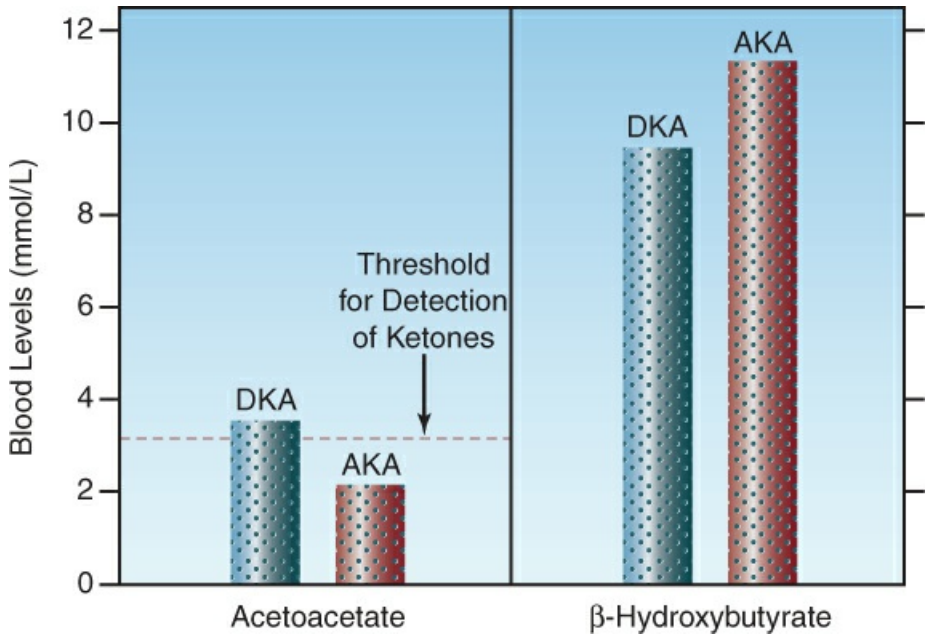

FIGURE 32.4 The concentrations of acetoacetate and β-hydroxybutyrate in the blood in diabetic ketoacidosis (DKA) and alcoholic ketoacidosis (AKA). The horizontal hatched line represents the minimum concentration of acetoacetate required to produce a positive nitroprusside reaction.

β-hydroxybutyrate Testing

There are now portable "ketone meters" that provide reliable measurements of β-OHB concentrations in fingerstick (capillary) blood in about 10 seconds (46). The American Diabetes Association considers measurements of plasma β-OHB with these meters as the preferred method for monitoring patients with diabetic ketoacidosis (47).

DIABETIC KETOACIDOSIS

Diabetic ketoacidosis (DKA) can be seen in patients with type 1 or type 2 diabetes, and there is no previous history of diabetes mellitus in up to 37% of cases (48). The most common precipitating factors in DKA are inappropriate insulin dosing and concurrent illness (e.g., infection). The mortality rate in DKA has decreased to ≤1% (49).

Clinical Features

The features of DKA proposed by the American Diabetes Association include a blood glucose >250 mg/dL, plasma HCO_3 <18 mEq/L, plasma pH ≤7.30, an elevated anion gap, and evidence of ketones in blood or urine (47). However, there are exceptions:

. The blood glucose is <250 mg/dL in about 3% of cases of DKA (49). This condition is known as *euglycemic diabetic ketoacidosis* (50) and it is most common in patients treated with sodium-glucose cotransporter-2 (SGLT2) inhibitors, and in pregnancy and starvation.

. Although uncommon, the anion gap can be normal in DKA (51). The renal excretion of ketones is accompanied by an increase in chloride reabsorption in the renal tubules, and the resulting hyperchloremia limits the increase in the anion gap.

Additional features of interest in DKA are as follows:

. Leukocytosis is not a reliable marker of infection in DKA because ketonemia produces a leukocytosis, which is proportional to the concentration of ketones in plasma (47). However, an increase in immature neutrophils (band forms) can be a reliable marker of infection in patients with DKA (52).

. Elevated troponin I levels without evidence of an acute coronary event has been reported in 27% of patients with DKA (53).

. Dehydration is almost universal in DKA, but this may not be reflected in the plasma sodium concentration because hyperglycemia has a dilutional effect on plasma sodium; i.e., the plasma sodium concentration decreases by 2.4 mEq/L for every 100 mg/dL increase in the plasma glucose concentration (54).

. Hyperglycemia also has a dilutional effect on the plasma chloride concentration, so the measured plasma sodium (not the corrected value) should be used to calculate the anion gap (55).

Management

The management of DKA is summarized in Table 32.3.

Volume Resuscitation

Volume deficits in DKA average 50–100 mL/kg (or 4–8 L for a 175 lb adult) (47). The traditional resuscitation fluid in DKA has been isotonic (“normal”) saline, but balanced salt solutions with a lower chloride concentration (e.g., Plasma-Lyte®, or Ringer’s lactate) have been shown to hasten resolution of the acidosis in DKA (56,57), and these fluids should be preferred to isotonic saline. In cases of euglycemic ketoacidosis, 5% dextrose should be added to all resuscitation fluids.

Volume resuscitation should begin at a rate of 15–20 mL/kg/hr (or 1 L/hour) for the first few

hours (47). When the patient stabilizes, the infusion rate can be decreased to 250 mL/hr. When the blood glucose falls to 250 mg/dL, change the intravenous fluid to 5% dextrose in 0.45% (half-normal) saline, and decrease the infusion rate to 150–200 mL/hr.

Insulin

Insulin therapy is started only when the plasma K^+ is >3.3 mEq/L (because insulin drives K^+ into cells). Regular insulin is given intravenously, starting with a bolus dose of 0.1 units per kilogram body weight and followed with a continuous infusion at 0.1 units/kg/hr. Because *insulin adsorbs to intravenous tubing*, the bolus insulin dose should be injected directly into the vein, and the initial 10 mL of infusate should be run through the IV setup before the insulin drip is started. The blood glucose levels should decrease by about 100 mg/dL per hour (49), and the insulin infusion should be adjusted to achieve this goal. When the blood glucose level falls to 250 mg/dL, the insulin infusion rate should be decreased to 0.05 units/kg/hr. Thereafter, the blood glucose levels should be maintained between 150–200 mg/dL. Achieving euglycemia is not recommended because of the risk of hypoglycemia.

The insulin infusion is continued until the acidosis resolves (i.e., the anion gap normalizes and the plasma HCO_3 is >18 mEq/L). Subcutaneous insulin can then be started, but the insulin infusion should be continued for at least one hour after the first subcutaneous dose. Patients who were insulin-dependent prior to admission can be placed on their usual outpatient regimen. Patients who are new to insulin should receive 0.5–0.8 Units/kg/day: half of this can be given as a long-acting preparation (e.g., glargine), and the remaining half as a short-acting preparation (e.g., lispro) in divided doses, to cover meals (49).

TABLE 32.3 Management of Diabetic Ketoacidosis

I. Intravenous Fluids

1. Start with a balanced crystalloid fluid (e.g., Ringer's lactate) and infuse at a rate of 15–20 mL/kg/hr (or 1 L/hr) for a few hours.
2. When patient stabilizes, decrease rate to 250 mL/hr.
3. When blood glucose falls to ≤250 mg/dL, change IV fluid to 5% dextrose in 0.45% saline and reduce rate to 150–200 mL/hr.
4. Continue IV fluids until patient can tolerate oral fluids.
5. ***Note:*** In cases of euglycemic ketoacidosis, 5% dextrose should be added to all IV fluids.

II. Insulin

1. Start insulin only if plasma K^+ >3.3 mEq/L.
2. Use regular insulin -start with a bolus of 0.1 U/kg, and inject directly into vein (insulin adsorbs to IV tubing). Then infuse at 0.1 U/kg/hr (run first 10 mL through IV tubing and discard).
3. Adjust rate, if needed, for a decrease in blood glucose of 100 mg/dL/hr.
4. When blood glucose falls to ≤250 mg/dL, decrease rate to 0.05 U/kg/hr.
5. Continue infusion until anion gap normalizes and plasma HCO_3 >18 mEq/L. Then transition to subQ insulin, but continue infusion for at least 1 hr after first subQ dose.

Potassium

Potassium depletion is universal in DKA, and the average deficit is 3–5 mEq/kg (58). However, the initial plasma K^+ is normal or elevated in 96% of patients with DKA because of the

concurrent acidosis (58). The presence of hypokalemia at presentation of DKA indicates severe potassium depletion.

The recommendations for K^+ replacement in DKA are shown in Table 32.4. It is important not to start insulin if the initial plasma K^+ is less than 3.3 mEq/L because insulin drives K^+ into cells, and this can precipitate life-threatening hypokalemia. Regardless of the initial potassium regimen, the plasma K^+ should be checked every 1–2 hours for the first 6 hours.

TABLE 32.4 Potassium Replacement in Diabetic Ketoacidosis

Plasma K^+	Recommendation
<3.3 mEq/L	Hold insulin infusion and give 40 mEq K^+ per hour IV until the plasma K^+ >3.3 mEq/L.
3.3–4.0 mEq/L	Give 20 mEq K^+ per hour IV.
4.0–5.5 mEq/L	Give 10 mEq K^+ per hour IV.
>5.5 mEq/L	Check plasma K^+ every 2 hours.

From Reference 49.

Phosphate

Phosphate depletion is also common in DKA, and averages 1–1.5 mmol/kg (58). However, phosphate replacement has no documented benefit in DKA, and is not recommended unless the phosphate level falls to <1 mg/dL (47,48,58). (See Chapter 38 for recommendations on phosphate repletion.)

Bicarbonate

Bicarbonate therapy has no documented benefit in DKA, and is not recommended as a routine measure (47,48).

Monitoring Acid-Base Status

Normalization of the anion gap is considered evidence that the ketonemia has resolved. The plasma HCO_3 can remain in the acidotic range if isotonic saline is used as the resuscitation fluid, because the high chloride concentration (154 mEq/L) creates a hyperchloremic (normal anion gap) metabolic acidosis that temporarily replaces the high anion gap acidosis from the ketonemia. This resolves when the intravenous infusion is slowed, and should not be a problem if balanced crystalloid fluids are used.

ALCOHOLIC KETOACIDOSIS

Alcoholic ketoacidosis (AKA) is a complex acid base disorder that occurs in chronic, malnourished alcoholics, and typically appears 1 to 3 days after a period of heavy binge drinking (59,60). Several mechanisms are involved, including reduced nutrient intake (which initiates lipolysis and ketogenesis), hepatic oxidation of ethanol (which generates NADH and enhances β-hydroxybutyrate and lactate formation), and dehydration (which impairs ketone excretion in the

urine).

Clinical Features

Patients with AKA appear debilitated, and typically present with nausea, vomiting, and abdominal pain (59). Electrolyte abnormalities are common, particularly the *hypo's* (e.g., hyponatremia, hypokalemia, hypophosphatemia, hypomagnesemia, hypoglycemia). Mixed acid base disorders are common in AKA, with a high anion gap metabolic acidosis from the ketonemia and mild elevations in plasma lactate, along with a metabolic alkalosis from vomiting. Acidemia is usually mild, and some patients are alkalemic (from protracted vomiting) (60).

Diagnosis

The diagnosis of AKA is suggested by the patient history (i.e., a debilitated alcoholic with a recent bout of binge drinking), along with evidence of dehydration, an elevated anion gap, and the presence of ketones in the blood or urine without hyperglycemia. However, *the nitroprusside reaction for detecting ketones can be negative in AKA*, as shown in Figure 32.4. The oxidation of ethanol in the liver generates NADH, and this favors the conversion of acetoacetate to β-hydroxybutyrate, which results in a low concentration of acetoacetate in blood and urine. Lactate elevations may be present, but are generally mild, and blood ethanol levels can be negative (59). Patients often present with abdominal pain, and pancreatitis should be ruled out.

Management

The management of AKA is notable for its simplicity; i.e., infusion of dextrose-containing saline solutions is usually all that is required. The glucose infusion is needed to correct the acidosis (59,60), while the infused volume corrects volume loss and promotes the renal clearance of ketones. The ketoacidosis usually resolves within 24 hours. Other electrolyte deficiencies are corrected as needed, and thiamine supplementation is recommended because glucose infusions can deplete marginal thiamine reserves (59). (See Chapter 48 for more on thiamine deficiency and replacement.)

A FINAL WORD

Don't Focus on the Acidosis

There are two points in this chapter that deserve emphasis:

. The problem with lactic acidosis and ketoacidosis is not the acidosis, but the underlying condition causing the problem. As a result, the management of these conditions should focus on correcting the underlying cause, and not correcting the acidosis.

. Bicarbonate is not a buffer in the physiological pH range, but is simply an end-product of CO_2 transport in blood. As such, it is an ineffective (and potentially harmful) alkalinizing agent.

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Chapter 33

Metabolic Alkalosis

The first step in the scientific method consists in being curious about the world.

Linus Pauling (*a*)

Although the spotlight usually falls on metabolic acidosis, the most common acid-base disturbance in hospitalized patients is metabolic *alkalosis* (1). The prevalence of metabolic alkalosis can be attributed to three factors: (a) common predisposing conditions, (b) the ability of alkalosis to sustain itself, and (c) the tendency for the condition to go unnoticed and untreated.

This chapter begins with an attempt to simplify the rather complex electrolyte involvement in metabolic alkalosis, and then describes an organized approach to the evaluation and management of metabolic alkalosis. Some comprehensive reviews of the topic are included in the bibliography at the end of the chapter (2,3).

PATHOGENESIS

Metabolic alkalosis is defined as an increase in the bicarbonate (HCO_3) concentration in venous blood to >30 mEq/L (2). The generation and maintenance of this condition involves several factors, including the state of the extracellular volume, the activity of aldosterone, the function of the kidneys, and the plasma chloride and potassium concentrations. Each of these factors is explained briefly in this section.

Bicarbonate Homeostasis

Under normal. steady state conditions, the concentration of bicarbonate in extracellular fluid is kept constant by the actions of the kidneys.

Bicarbonate Reabsorption

About 4,000–4,500 mEq of bicarbonate (HCO_3) is filtered daily in the kidneys (2), and all of it is reclaimed by the renal tubules. Most (85–90%) of the filtered HCO_3 is reabsorbed in the proximal tubules, which is also the major site for sodium reabsorption. The remaining 10–15%

of the filtered HCO_3 is reabsorbed by specialized cells in the collecting ducts, and the mechanism for this is shown in the middle cell in Figure 33.1. (Note that chloride moves out of the blood in exchange for HCO_3.) These cells also secrete H^+ into the tubular lumen, which is then excreted as ammonium.

Bicarbonate Secretion

There are other specialized cells in the collecting ducts that are involved in HCO_3 secretion via a chloride-bicarbonate exchange protein (called *pendrin*) that is on the luminal surface of the cells (see the lower cell in Figure 33.1). This process is only minimally active under normal conditions, but the pendrin gene is up-regulated in metabolic alkalosis, to help clear the excess HCO_3 (4).

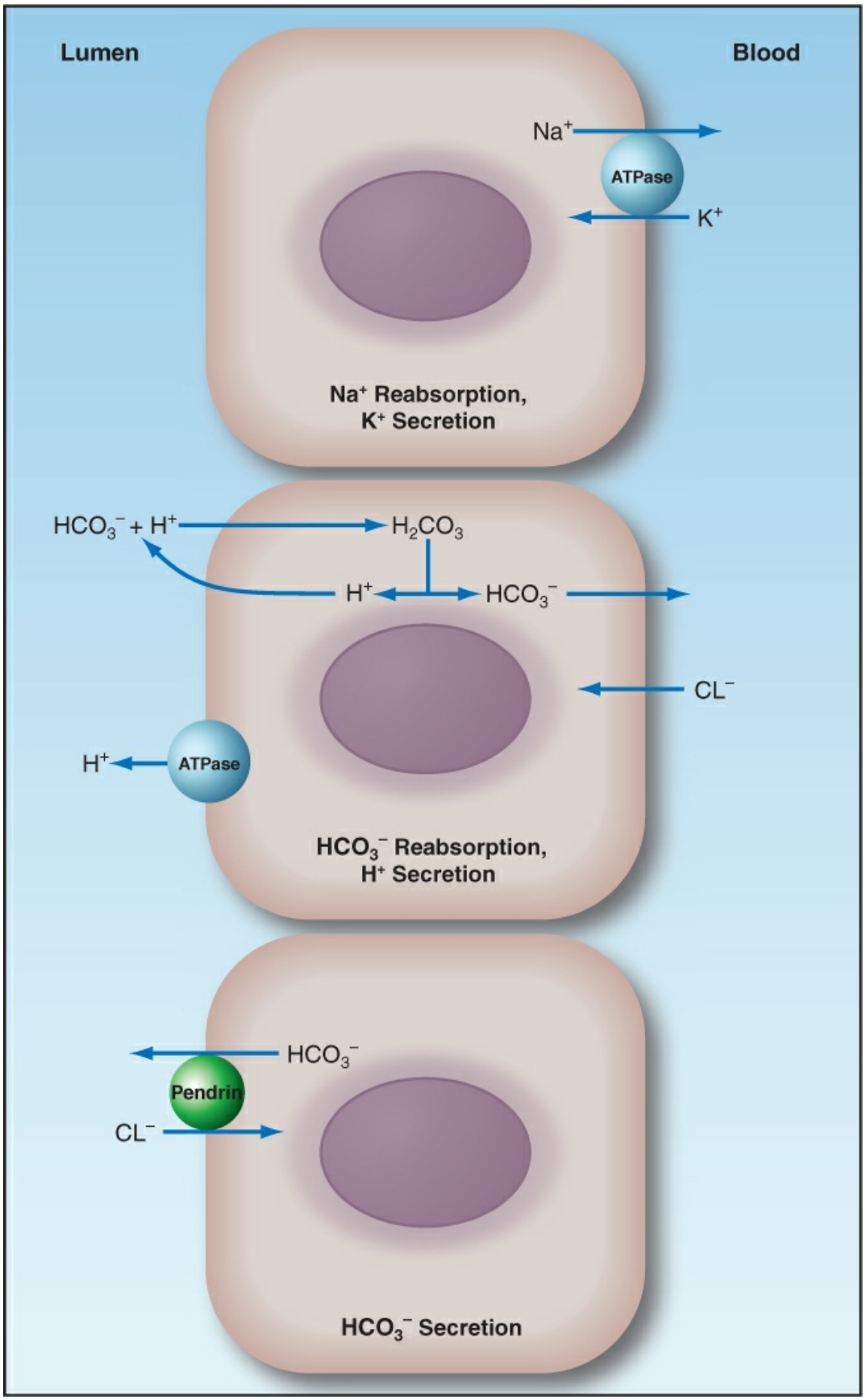
Lumen
Blood
Na+
ATPase
K+
Na+ Reabsorption,
K+ Secretion
HCO3− + H+
H2CO3
H+
HCO3−
CL−
H+
ATPase
HCO3− Reabsorption,
H+ Secretion
HCO3−
Pendrin
CL−
HCO3− Secretion

FIGURE 33.1 Specialized cells in the collecting ducts of the kidneys that are involved in acid-base balance. See text for explanation.

Conditions That Promote Metabolic Alkalosis

Several conditions promote the production and maintenance of metabolic alkalosis, as briefly summarized here.

Loss of Gastric Acid

Gastric secretions are rich in hydrogen ions (50–100 mEq/L), chloride (120–160 mEq/L), and to a lesser degree, potassium (10–15 mEq/L) (5). Loss of H^+ in gastric secretions generates an equimolar addition of HCO_3 to the extracellular fluid, which creates a metabolic alkalosis. Loss of chloride and potassium will help to sustain the alkalosis, by mechanisms described later.

Hypovolemia

Many causes of metabolic alkalosis are associated with a decrease in extracellular (plasma) volume. This condition promotes metabolic alkalosis in two ways. First, there is a decrease in glomerular filtration rate, which results in a decrease in filtered HCO_3. Secondly, the decrease in renal perfusion stimulates the renin-angiotensin-aldosterone system, and the aldosterone promotes metabolic alkalosis by mechanisms described next. (*Note:* The metabolic alkalosis associated with hypovolemia is often called "contraction alkalosis", but this is a misnomer because it implies that the problem is a decrease in free water rather than an excess of HCO_3.)

Aldosterone

Aldosterone is a mineralocorticoid produced in the adrenal cortex that stimulates a sodium-potassium exchange pump in the renal collecting ducts (depicted by the uppermost cell in Figure 33.1) to promote Na^+ reabsorption and K^+ secretion. This can lead to K^+ depletion, which promotes metabolic alkalosis by mechanisms described later. Aldosterone also stimulates the membrane ATPase pump responsible for H^+ secretion into the renal tubules (see the middle cell in Figure 33.1) (6).

Chloride Depletion

Chloride depletion plays a major role in promoting metabolic alkalosis by increasing HCO_3 reabsorption and inhibiting HCO_3 secretion in the renal collecting ducts (2,3). Both effects are mediated by a decrease in luminal chloride concentration. The inhibition of HCO_3 secretion is due to inhibition of the anion exchange protein, pendrin, which is the principal mechanism for the ability of chloride depletion to promote metabolic alkalosis (7).

Hypokalemia

Hypokalemia promotes metabolic alkalosis via a transcellular shift of H^+ into cells (in exchange for a shift of K^+ out of cells). The resulting decrease in intracellular pH in renal tubular cells also promotes HCO_3 reabsorption (8).

Diuretics

Thiazide diuretics and "loop" diuretics like furosemide promote metabolic alkalosis via chloride

and K^+ depletion. The principal action of these diuretics is to increase sodium loss in the urine, and urinary chloride excretion usually matches sodium excretion, so this can lead to chloride depletion The increased Na^+ delivery to the distal tubules also promotes K^+ loss via a Na^+–K^+ exchange pump (see the cell at the top in Figure 33.1).

CLINICAL CONSEQUENCES

Metabolic alkalosis is clinically silent in most patients. Severe alkalosis can be accompanied by neurologic manifestations and hypoventilation, but these are rarely life-threatening. In one remarkable case report, an elderly patient with protracted vomiting and a plasma [HCO_3] of 151 mEq/L was hemodynamically stable, and recovered uneventfully after volume and electrolyte replacement (9).

Neurologic Manifestations

The neurologic manifestations attributed to alkalosis include depressed consciousness, generalized seizures, paresthesias, and carpopedal spasms, but these are usually associated with *respiratory alkalosis*, not metabolic alkalosis.

Hypoventilation

The ventilatory response to metabolic alkalosis is hypoventilation, with a subsequent rise in arterial PCO_2. However, this is not a vigorous response, and a considerable rise in plasma HCO_3 may be necessary to produce significant CO_2 retention (10).

The ventilatory response to metabolic alkalosis is described by the following equation (11):

$$\Delta\ PaCO_2 = 0.7 \times \Delta\ HCO_3 \qquad (33.1)$$

where $PaCO_2$ is the arterial PCO_2 and HCO_3 is the plasma (usually venous) HCO_3 concentration. This equation was used to construct the curve in Figure 33.2 showing the relationship between $PaCO_2$ and plasma HCO_3 in progressive metabolic alkalosis. Note that hypercapnia (i.e., $PaCO_2$ > 46 mm Hg) does not occur until the plasma HCO_3 increases almost 10 mEq/L (which represents a 40% increase in plasma HCO_3) and that worrisome hypercapnia (i.e., $PaCO_2$ > 50 mm Hg) does not occur until the metabolic alkalosis is severe.

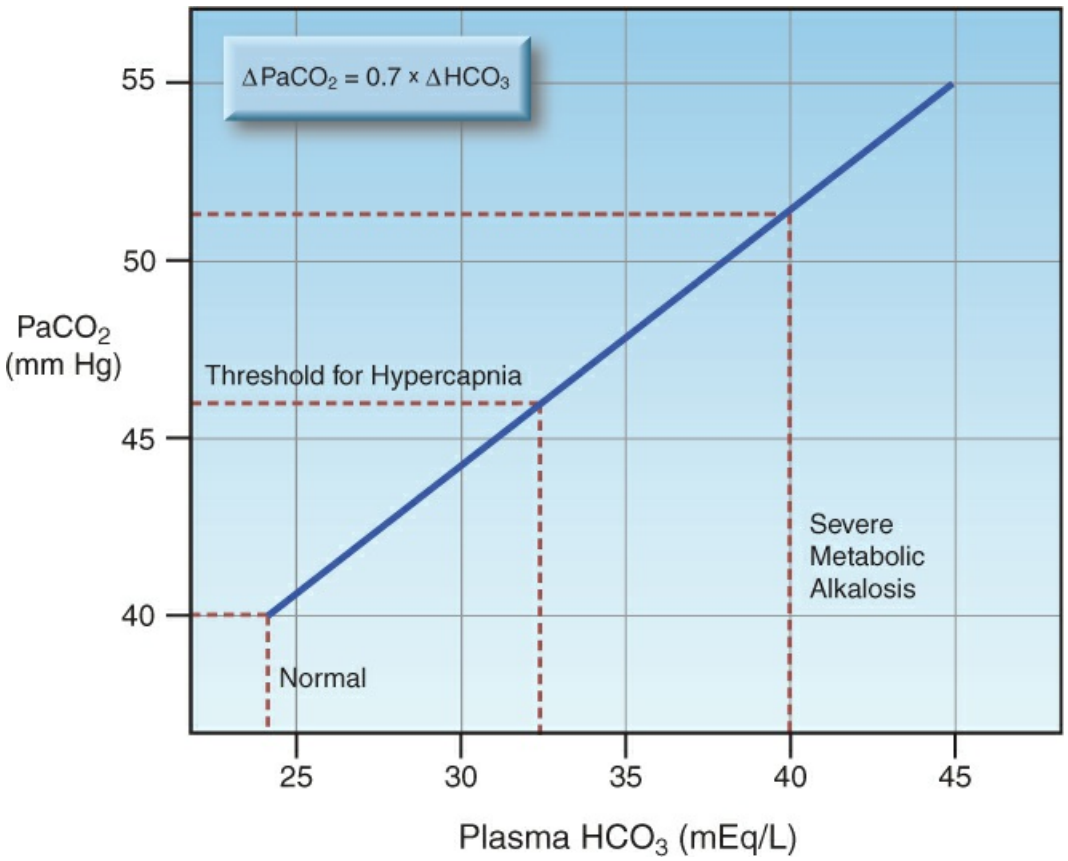

FIGURE 33.2 The relationship between plasma bicarbonate (HCO_3) and arterial PCO_2 ($PaCO_2$) in metabolic alkalosis, as predicted by the equation shown at the top of the graph. Note that the plasma HCO_3 must increase almost 10 mEq/L to produce hypercapnia ($PaCO_2$ > 46 mm Hg), and that worrisome hypercapnia (i.e., $PaCO_2$ > 50 mm Hg) does not occur until the alkalosis is severe.

Oxyhemoglobin Dissociation Curve

Alkalosis shifts the oxyhemoglobin dissociation curve to the left (Bohr effect), which results in a decreased tendency for hemoglobin to release oxygen into the tissues. When the O_2 extraction from capillary blood is constant, a leftward shift of the oxyhemoglobin dissociation curve results in a decrease in venous PO_2 (12), which typically indicates a decrease in tissue PO_2. However, there is no evidence of inadequate tissue oxygenation from this effect.

EVALUATION

The conditions that promote metabolic alkalosis can be organized according to the state of the extracellular volume, and the urinary chloride concentration, as shown in Table 33.1 (2,3).

TABLE 33.1 Principal Sources of Metabolic Alkalosis

Extracellular Volume	Urine Chloride	Conditions
Low	<20 mEq/L	Vomiting, NG Suction

		Thiazide or Loop Diuretics (after-effect) Laxative Abuse
High	>20 mEq/L	Primary Hyperaldosteronism Exogenous Mineralocorticoids Licorice Ingestion
Variable	Variable	K^+ Depletion Mg^{++} Depletion

Low ECV, Low Urine CL

Metabolic alkalosis associated with a low extracellular volume (ECV) and a low urinary chloride concentration (<20 mEq/L) is also called *chloride-sensitive metabolic alkalosis* (2,3). This is the usual type of metabolic alkalosis in ICU patients, and can be the result of gastric acid loss (from vomiting or nasogastric suction), secondary hyperaldosteronism (from hypovolemia), or excessive use of thiazide or loop diuretics (e.g., furosemide). The diuretic effect must be dissipated for the urine chloride to be low.

Laxative Abuse

Diarrhea usually produces a hyperchloremic metabolic acidosis from bicarbonate losses in stool, but the diarrhea associated with chronic laxative abuse is rich in potassium and chloride (70–90 mEq/L), and typically results in a metabolic alkalosis with a low ECV and a low urinary chloride (13). The diagnosis can be elusive, because patients often deny laxative abuse.

High ECV, High Urine CL

Metabolic alkalosis associated with an increased ECV and a high urinary chloride concentration (>20 mEq/L) is also called *chloride-resistant metabolic alkalosis*, and the principal cause is primary hyperaldosteronism. This is an unlikely cause of metabolic alkalosis in the ICU, and is typically the result of aldosterone-producing adrenal adenomas or idiopathic adrenal hyperplasia (14). Analogous conditions include chronic ingestion of licorice, and exogenous mineralocorticoid excess (2,3).

Other Causes

Hypokalemia and hypomagnesemia can cause a metabolic alkalosis in which the extracellular volume status and urinary chloride concentration are variable (3,15).

MANAGEMENT

The management of metabolic alkalosis with a low ECV and a low urinary chloride (i.e., chloride-responsive metabolic alkalosis) involves replenishment of chloride and potassium with isotonic saline and potassium chloride.

Isotonic Saline

The volume of isotonic saline needed to correct a metabolic alkalosis can be estimated by first

estimating the chloride (CL^-) deficit, as shown below (16,17):

$$CL^- \text{ deficit (mEq)} = 0.2 \times \text{wt (kg)} \times (100 - \text{plasma } CL^-) \quad (33.2)$$

where wt is lean body weight in kg, and 100 is the desired plasma chloride concentration (in mEq/L). The required volume of isotonic saline (in liters) is then estimated as follows:

$$\text{Volume of isotonic saline (L)} = CL^- \text{ deficit}/154 \quad (33.3)$$

where 154 is the chloride concentration (in mEq/L) in isotonic saline. This method is summarized in Table 33.2. Rapid saline infusion is not necessary, and a rate of 100 mL/hr above hourly fluid losses is appropriate.

EXAMPLE: A 70 kg adult with protracted vomiting has a metabolic alkalosis with a plasma chloride of 80 mEq/L. The chloride deficit in this case is 0.2 × 70 × (100–80) = 280 mEq. The volume of isotonic saline needed to correct this deficit is 280/154 = 1.8 liters.

TABLE 33.2 Saline Infusions for Metabolic Alkalosis

Step 1. Estimate the chloride deficit:

$$CL^- \text{ deficit (mEq)} = 0.2 \times \text{wt (kg)} \times (100 - \text{plasma } CL^-)$$

Step 2. Determine the replacement volume of isotonic saline:

$$\text{Volume of 0.9\% NaCL (L)} = \frac{CL^- \text{ deficit}}{154}$$

Step 3. Rate of replacement: 100 mL/hr above hourly fluid losses

From References 16 and 17.

Potassium Chloride

Potassium replacement with KCL may be needed in addition to saline infusions. However it important to emphasize that *diuretic-induced hypokalemia can be resistant to potassium replacement if there is concurrent magnesium depletion* (18). Since magnesium depletion is also common during diuretic therapy, the plasma magnesium level should be checked before starting K^+ replacement in patients receiving diuretics. (The evaluation and management of magnesium depletion is described in Chapter 37.)

Edematous States

Patients with edema from heart failure, cirrhosis, or cor pulmonale can have a metabolic

alkalosis from diuretic therapy. In these cases, saline infusion is counterproductive, and K^+ replacement is used to correct the alkalosis. These patients can also benefit from acetazolamide, as described next.

Acetazolamide

Acetazolamide (Diamox) is a carbonic anhydrase inhibitor that inhibits HCO_3 reabsorption in the proximal tubules. The increase in HCO_3 excretion is accompanied by an increase in Na^+ excretion (as $NaHCO_3$), so acetazolamide also acts as a diuretic, which is advantageous in edematous states associated with a metabolic alkalosis. The recommended dose is 250 to 375 mg IV or PO, once or twice daily (19).

Hydrochloric Acid Infusion

Severe metabolic alkalosis that is not corrected with K^+ replacement and acetazolamide can be treated with an infusion of dilute hydrochloric acid, but this can be risky, and is reserved only for patients with severe alkalosis (plasma $HCO_3 > 50$ mEq/L or pH > 7.55).

METHOD: The dose of HCL is determined by estimating the H^+ deficit with the equation below (see also Table 33.3) (19).

$$H^+ \text{ Deficit (mEq)} = 0.5 \times \text{wt (kg)} \times (\text{plasma } HCO_3 - 24) \quad (33.4)$$

where wt is the lean body weight in kg, and 24 is the normal plasma HCO_3.

TABLE 33.3 Hydrochloric Acid Infusions

Step 1. Estimate the hydrogen ion deficit:

$$H^+ \text{ deficit (mEq)} = 0.5 \times \text{wt (kg)} \times (\text{plasma } HCO_3^- - 24)$$

Step 2. Determine the replacement value of HCL:

$$\text{Liters of 0.1N HCL} = \frac{H^+ \text{ deficit}}{100}$$

Step 3. Rate of replacement: ≤0.2 mEq/kg/hr

From References 16 and 17.

The HCL solution is prepared by adding 100 mL of 1 normal (1N) HCL to 900 mL of isotonic saline or sterile water, which makes a 0.1N HCL solution (100 mEq H^+/L) The volume of 0.1N HCL (in liters) needed to correct the H^+ deficit is determined by the ratio (H^+ deficit/100), as shown in Table 33.3. Because HCL solutions are corrosive, they *should be infused through a large, central vein* (20), and *the infusion rate should not exceed 0.2 mEq/kg/hr*

(17). The entire H^+ deficit does not have to be replaced; i.e., the HCL infusion can be stopped when the plasma pH falls to acceptable levels (e.g., <7.5).

ADVERSE EFFECTS: The major concern with HCL infusions is the corrosive effect on blood vessels. Extravasation of HCL solutions can produce severe tissue necrosis, even when the solution is infused through a central vein (21).

A FINAL WORD

Spotlight on Chloride

Chloride is the second most abundant electrolyte in the extracellular fluid, and has emerged as a major factor in metabolic acid-base disorders, including both metabolic alkalosis (via chloride depletion) and metabolic acidosis (i.e., hyperchloremic metabolic acidosis). It also plays a major role in determining the extracellular volume (which is described in Chapter 35).

In recognition of its importance in acid-base balance and volume regulation, chloride has been given the title "queen of electrolytes" (22), emphasizing that chloride is much more than an inconsequential partner for sodium in the extracellular fluid.

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Section XI

RENAL & ELECTROLYTE DISORDERS

A man is a bundle of relations.

Ralph Waldo Emerson
(1841)

Chapter 34

Acute Kidney Injury

You can never solve all difficulties at once.

Paul A.M. Dirac (*a*)

As many as 60% of ICU patients experience an acute deterioration in renal function, which has been given the umbrella term, *acute kidney injury* (1). As expected, this condition has a multitude of etiologies, but most of the inciting factors can be classified as inflammatory, ischemic, or nephrotoxic in nature (2,3). The consequences of this condition are as varied as the etiologies, but about 15% of the patients require renal replacement therapy (4), and as many as 60% of the patients will not survive (5).

This chapter begins by presenting the diagnostic criteria for acute kidney injury (including the shortcomings), then proceeds with a description of the most common inciting conditions, and finishes with a description of the renal replacement therapies. Some authoritative reviews of this rather massive topic are included in the bibliography at the end of the chapter (2–4).

DIAGNOSTIC CRITERIA

The term "acute renal failure" was introduced in 1951 (5), but due to a lack of agreement about this condition, the term "acute kidney injury" (AKI) was introduced in 2002, and ten years later (in 2012), the defining criteria for AKI were adopted and published as the "Kidney Disease Improving Global Outcomes (KDIGO) guidelines (6), which are shown in Table 34.1.

TABLE 34.1 Diagnostic Criteria for Acute Kidney Injury

The diagnosis of acute kidney injury (AKI) requires one of the following conditions:

1. An increase in serum creatinine of ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours.
2. An increase in serum creatinine to ≥1.5 times baseline within the previous 7 days.
3. Urine volume <0.5 mL/kg/hr (ideal body weight) for 6 hours.

From Reference 6.

Limitations

There are a number of limitations in the diagnostic criteria for AKI, and the major ones are listed below:

. The presence of oliguria (urine output <0.5 mL/kg/hr) can be an appropriate renal adjustment to decreased renal perfusion, rather than a sign of kidney "injury".

. There is a lack of agreement about the minimum increase in serum creatinine required for the diagnosis of acute kidney injury.

. The baseline serum creatinine may not be known.

. The serum creatinine can be misleading as a marker of the glomerular filtration rate, as described next.

Serum Creatinine

The serum creatinine is the traditional marker of the glomerular filtration rate (GFR), and Figure 34.1 shows the popular creatinine-based methods for estimating the GFR. However, the serum creatinine level has the following limitations as a marker of the GFR:

. The creatinine in blood is derived from the creatine produced in muscle, and thus is influenced by muscle mass, and the rate of creatine production in muscle.

. The serum creatinine concentration is influenced by changes in plasma volume.

. Creatinine is not only filtered at the glomerulus, but is also secreted by the renal tubules.

The influence of creatine production in muscle is an important consideration because critically ill patients lose about 2% of their muscle mass each day (7), and a decreased rate of creatine production has been reported in sepsis (8), which is the most common cause of AKI (see later). As a result, the serum creatinine can be an unreliable marker of the GFR in critically ill patients. This is supported by studies showing that *estimates of the GFR based on the serum creatinine level consistently overestimate the true GFR in critically ill patients* (9,10). This has important implications not only for the evaluation of renal function, but also for the appropriate dosing of drugs based on estimates of the GFR.

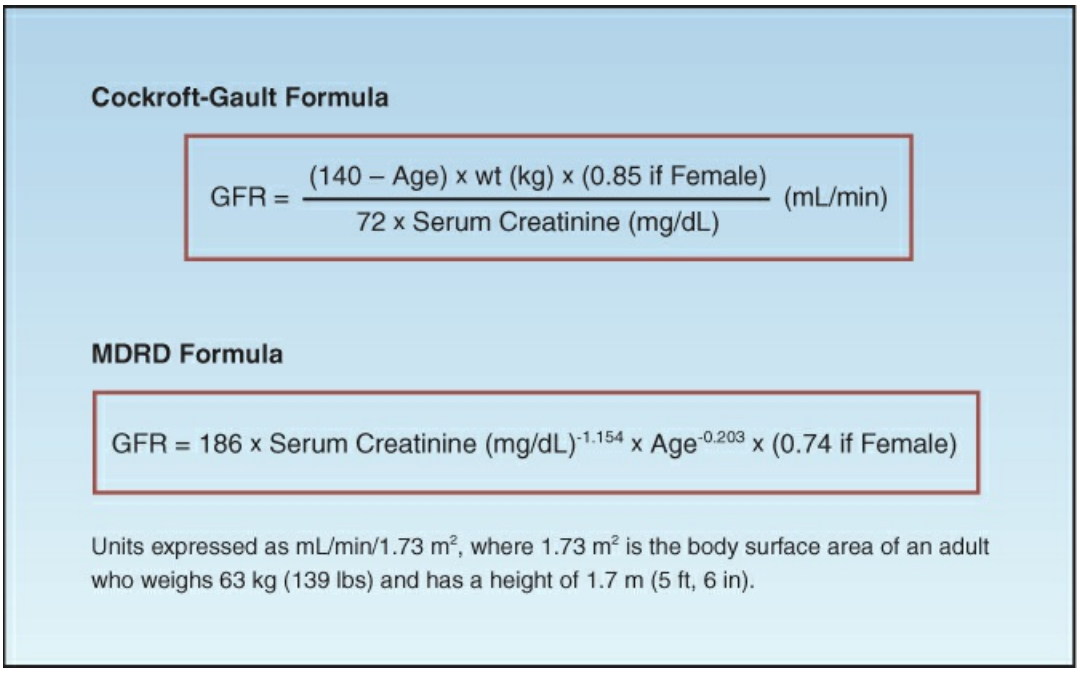

FIGURE 34.1 Popular formulas for estimating the glomerular filtration rate (GFR) based on the serum creatinine level. MDRD = Modification of Diet in Renal Disease.

CYSTATIN C: Cystatin C is a protein produced by most cells in the body that is completely cleared by the GFR. Serum levels of cystatin C are not influenced by muscle mass, which gives cystatin a potential advantage over creatinine. Estimates of the GFR based on the serum cystatin C level are more accurate than creatinine-based estimates, but they often underestimate the true GFR in critically ill patients (9,10). Combining cystatin-based and creatinine-based estimates of GFR increases the accuracy further (9,10), but the complexity of this approach is far from appealing.

Other Monikers

Acute kidney injury that persists for more than a few days is called *acute kidney disease*, and if this condition persists for ≥90 days, it is called *chronic kidney disease* (5). The reasoning for these distinctions is unclear (i.e., injury vs. disease, and 90 days vs. 60 days)

COMMON CAUSES OF ACUTE KIDNEY INJURY

As mentioned in the introduction, most cases of AKI are the result of inflammatory injury, hemodynamic aberrations, or a nephrotoxic agent, and Table 34.2 shows the common causes of AKI in each of these categories.

TABLE 34.2 Common Causes of Acute Kidney Injury

Mechanism	Conditions
Inflammation	Major Surgery Multisystem Trauma Sepsis†

Hemodynamic Compromise	Cardiac Arrest Heart Failure Hemorrhage Increased Abdominal Pressure Liver Failure
Nephrotoxic	Radiocontrast Dye Rhabdomyolysis Nephrotoxic Drugs & Toxins

†The leading cause of acute kidney injury.

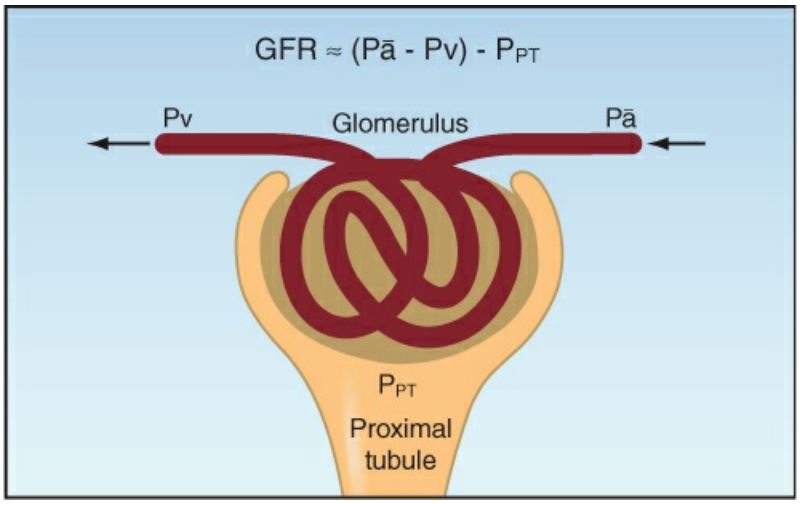

FIGURE 34.2 Schematic depiction of the pressures that influence the glomerular filtration rate (GFR). Pā = mean arterial pressure, Pv = venous pressure, P_{PT} = pressure in the proximal tubules.

Relevant Pressures

Before describing the common causes of AKI, a quick review of the pressures that influence the glomerular filtration rate (GFR) is warranted. This is illustrated in Figure 34.2. Flow through the glomerulus is determined by the difference between the mean arterial pressure and the renal venous pressure (Pā – Pv). This is also called the *glomerular filtration pressure*. The net filtration pressure across the glomerulus, which is also called the *filtration gradient*, is the difference between the glomerular filtration pressure and the pressure in the proximal renal tubules (P_{PT}); i.e.,

$$\text{Filtration Gradient} = (\text{Pā} - \text{Pv}) - P_{PT} \qquad (34.1)$$

These relationships predict that the GFR will decrease not only when there is a decrease in mean arterial pressure, but also when there is an increase in venous pressure (i.e., renal venous pressure or central venous pressure) or an increase in pressure in the proximal tubules.

Sepsis

Sepsis is the leading cause of AKI, and is responsible for about half of the cases of AKI in the

ICU population (3). The principal mechanism is inflammatory (oxidative) injury involving both the capillary endothelium in the glomerulus and the epithelial lining of the renal tubules (11). The renal tubular injury is also called *acute tubular necrosis* (ATN), and is characterized by sloughing of the damaged cells into the lumen of the renal tubules, as shown in Figure 34.3 (12). This creates a luminal obstruction, which increases the pressure in the proximal tubules, and hence decreases the GFR (according to Figure 34.2). This phenomenon is called *tubuloglomerular feedback* (13).

Major surgery and multisystem trauma are other causes of AKI in which inflammation plays a major role (although hemodynamic factors may also be involved). AKI has been reported in over 50% of patients after liver transplantation, in 18% of patients following cardiac surgery, and in 13% of patients undergoing major abdominal surgery (3). Multisystem trauma is accompanied by AKI in about 30% of cases, and rhabdomyolysis is responsible for 30% of these cases (14).

Cardiorenal Syndrome

Heart failure and renal dysfunction are common companions; i.e., in a review that included about 80,000 hospitalized patients with heart failure, renal dysfunction was present in 63% of the patients (15). This association between heart failure and renal impairment is known as the *cardiorenal syndrome* (16).

Venous Congestion

The renal impairment associated with heart failure has traditionally been attributed to a decrease in renal perfusion pressure, but the increase in central venous pressure in heart failure also plays a role in reducing the GFR (17). In fact, in a study of patients with heart failure who were managed with pulmonary artery catheters, the right atrial pressure (central venous pressure) was the only parameter that showed a correlation with renal dysfunction (18). It seems likely that a decrease in renal perfusion pressure plays a major role in the renal dysfunction associated with acute heart failure, while venous congestion assumes an important role in cases of chronic, decompensated heart failure (19).

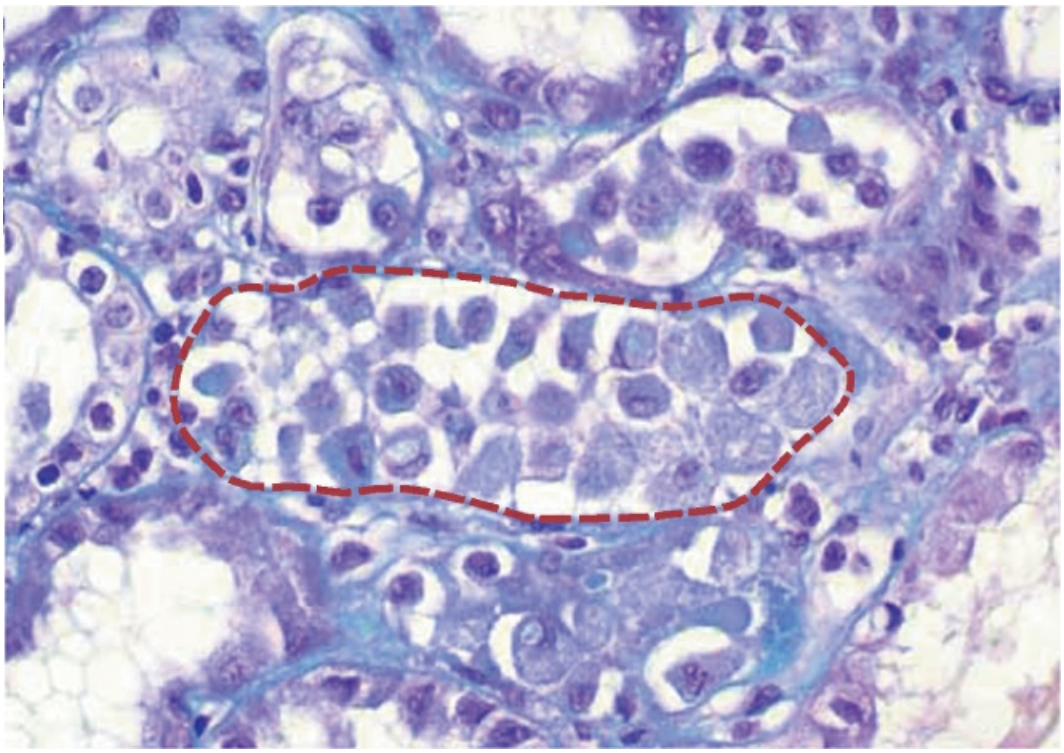

FIGURE 34.3 Photomicrograph of acute tubular necrosis (ATN) showing a proximal tubule (outlined by the dotted line) filled with exfoliated renal tubular cells. Image retouched, from Reference 12.

The influence of venous pressure on the GFR means that AKI can be the result of any disorder that results in pulmonary hypertension and right heart failure. The abdominal compartment syndrome is another cause of AKI mediated by venous pressure, as explained next.

Abdominal Compartment Syndrome

Abdominal compartment syndrome (ACS) is an increase in intra-abdominal pressure that is great enough to cause dysfunction in one or more vital organs (20). The organ dysfunction usually involves the bowel, kidneys, and/or cardiovascular system. *ACS is more common than suspected in critically ill patients, and is often overlooked as a cause of AKI in ICU patients* (21).

Relevant Pressures

The intra-abdominal pressure (IAP) is normally 5–7 mm Hg in the supine position. Intra-abdominal hypertension (IAH) is defined as a supine IAP ≥ 12 mm Hg, and ACS is defined as a supine IAP > 20 mm Hg that is associated with AKI or acute dysfunction in another organ systems.

ABDOMINAL PERFUSION PRESSURE: As shown in Figure 34.2, the driving pressure for glomerular blood flow is the difference between the mean arterial pressure and the pressure in the renal veins (Pā – Pv). However, when IAP exceeds the renal venous pressure, the driving pressure for glomerular flow is the difference between the mean arterial pressure and the IAP. This pressure difference is called the *abdominal perfusion pressure* (APP):

$$APP = P\bar{a} - IAP \quad (34.2)$$

The APP needed to preserve renal blood flow is not well defined, but studies of patients with IAH and ACS have shown that an APP > 60 mm Hg is associated with improved outcomes (20).

FILTRATION GRADIENT: When the IAP is increased, the pressure in the proximal tubules is considered equivalent to the IAP, so the filtration gradient is determined as follows:

$$\text{Filtration Gradient} = P\bar{a} - (IAP \times 2) \quad (34.3)$$

This relationship predicts that an increase in IAP will have a greater impact on the GFR than an equivalent decrease in arterial pressure. This might explain why *oliguria is one of the first signs of ACS* (20).

Predisposing Conditions

ACS is traditionally associated with abdominal trauma or surgery, but several medical conditions can raise the IAP and predispose to ACS, including gastric distension, bowel obstruction, ileus, ascites, bowel wall edema, hepatomegaly, positive-pressure breathing, upright body position, and obesity (22). Several of these factors can co-exist in critically ill patients, which explains why *IAH is discovered in as many as 60% of patients in medical and surgical ICUs* (23).

CRYSTALLOID RESUSCITATION: One of the more common and unrecognized causes of IAH is volume resuscitation with crystalloid fluids, which can raise the IAP by promoting edema in the abdominal organs (especially the bowel). (The distribution of crystalloid fluids is described in Chapter 10: see Figure 10.1.) In one report of ICU patients with a positive fluid balance >5 liters over 24 hours, IAH was present in 85% of the patients, and ACS was diagnosed in 25% of the patients (24). This observation adds to the growing consensus that avoiding a positive fluid balance will reduce morbidity and mortality during the ICU stay. (See Chapter 11 for more on the concerns about fluid accumulation.)

Measuring Intra-abdominal Pressure

The physical examination is insensitive for detecting increases in IAP (25), so IAP must be measured. The standard measure of IAP is the pressure in a decompressed urinary bladder, which is measured with specialized bladder drainage catheters. The following conditions are required for each measurement (20): (*a*) the patient must be in the supine position, with the pressure transducer zeroed in the mid-axillary line, (*b*) a small volume (25 mL) of isotonic saline is injected into the bladder 30–60 seconds prior to each measurement, and (*c*) the IAP is measured only at the end of expiration, and only when there is no evidence of abdominal muscle contractions. The IAP is measured in mm Hg, not cm H_2O (1 mm Hg = 1.36 cm H_2O).

Hepatorenal Syndrome

Acute kidney injury has been reported in 50% of patients with end-stage liver disease (26). The AKI in this setting can be the result of hypovolemia or sepsis (especially spontaneous bacterial peritonitis), or it can be a manifestation of the *hepatorenal syndrome* (HRS), a serious condition caused by the diversion of blood flow away from the kidneys due to the combination of renal

vasoconstriction and splanchnic vasodilation (27). The diagnosis of HRS is suggested by excluding hypovolemia and sepsis as a cause of AKI, and the urinary indices (described later) can distinguish HRS from ATN.

HRS typically carries a very poor prognosis, with liver transplantation being the definitive treatment. There is, however, a short-term management strategy, which is presented in Chapter 39.

Nephrotoxins

A variety of drugs can precipitate AKI, as shown in Table 34.3, and avoiding these (or any) drugs is always wise when possible (28).

TABLE 34.3 Drugs Most Often Implicated in Acute Kidney Injury

Mechanism	Offending Drugs
Altered Renal Hemodynamics	*Most Cited:* Nonsteroidal anti-inflammatory agents (NSAIDs) *Others:* ACE inhibitors, angiotensin receptor blockers, cyclosporine, tacrolimus
Osmotic Nephropathy	*Most Cited:* Hydroxyethyl starches *Others:* Mannitol, intravenous immunoglobulins
Renal Tubular Injury	*Most Cited:* Aminoglycosides *Others:* Amphotericin B, antiretrovirals, cisplatin
Interstitial Nephritis	*Most Cited:* Antimicrobials (penicillins, cephalosporins, sulfonamides, vancomycin, macrolides) *Others:* Anticonvulsants (phenytoin, valproic acid), H_2 blockers, NSAIDs, proton pump inhibitors

Adapted from Reference 28.

Radiocontrast Dye

Iodinated contrast agents have traditionally been perceived as a cause of AKI in critically ill patients, but this was based on observational studies. More recent and better controlled studies have revealed that *radiocontrast dye injections do not increase the incidence of AKI in critically ill patients* (29), *and they do not worsen renal function in patients with pre-existing AKI* (30). However, iodinated contrast dye is still considered risky in patients with chronic kidney disease and a GFR < 30 mL/min/1.73 m^2 (31).

PROPHYLACTIC FLUIDS: Despite the favorable data on radiocontrast agents, the most recent consensus statement includes the following recommendations (31).

. Prophylactic saline infusions are recommended for radiocontrast dye injections in patients with AKI, or with an estimated GFR < 30 mL/min/1.73 m^2. This recommendation does not necessarily apply to patients with heart failure.

. The infusion should begin 1 hour prior to the study, and should continue for 3–12 hours after the study. There is no firm recommendation regarding the volume infused.

Rhabdomyolysis

AKI is the most serious complication of diffuse muscle injury (rhabdomyolysis). The culprit is myoglobin, which is released by the injured muscle and is capable of damaging the renal tubular epithethial cells (32,33). The source of this injury may be the iron moiety in heme, which is capable of oxidative cell injury via the production of hydroxyl radicals (see Figure 25.6).

DIAGNOSIS: The diagnosis of AKI can be difficult in the setting of rhabdomyolysis because the injured muscle releases creatine, which elevates the serum creatinine level. Elevation of the creatine kinase (CK) in blood is essential for the diagnosis of rhabdomyolysis, but the CK level correlates more with the severity of the muscle injury than the risk of AKI (32). The presence of myoglobinuria is thus a critical component of diagnosing AKI in patients with rhabdomyolysis. A urine myoglobin level >20 μg/L is evidence of significant myoglobinuria (urine usually begins to turn brown at this level) (33).

Myoglobin can also be detected in urine with the orthotoluidine dipstick reaction (Hemastix), which is used to detect occult blood in urine. If the test is positive, the urine should be centrifuged (to separate erythrocytes) and the supernatant should be passed through a micropore filter (to remove hemoglobin). A persistently positive test after these measures is evidence of myoglobin in urine. An alternative approach is to inspect the urine sediment for red blood cells; i.e., a positive dipstick test for blood without red blood cells in the urine sediment can be used as evidence of myoglobinuria.

MANAGEMENT: The following measures are available for preventing or limiting myoglobinuric renal injury (32,33).

. Aggressive volume resuscitation to promote renal tubular flow is the most effective measure for preventing or limiting myoglobin nephrotoxicity. Isotonic saline can be given in volume of 10–20 mL/kg initially, and then infused to maintain a urine output of at least 1 mg/kg/hr. However, if oliguria persists after a few hours, it is important to abandon this strategy to prevent fluid overload.

. Alkalinization of the urine to a pH > 6.5 with bicarbonate infusions can inhibit cast formation in the renal tubules, but this is difficult to accomplish, and bicarbonate has its own problems (see Chapter 32).

. Diuresis with mannitol or furosemide has been used to promote renal tubular flow, but diuresis is risky because it is counterproductive to the planned volume resuscitation.

As many as 30% of patients will require renal replacement therapy (34), which is described later in the chapter.

DIAGNOSTIC CONSIDERATIONS

The following measures can be helpful if there is uncertainty about the diagnosis of AKI or its source.

Ultrasound

A beside ultrasound can be useful for uncovering chronic kidney disease (i.e., small kidneys),

and for identifying post-renal obstruction (i.e., hydronephrosis). This latter condition is especially important, as emergent drainage may be necessary, especially if the urine is infected.

Urinary Indices

The measures in Table 34.4 can help to determine if the source of AKI is renal hypoperfusion (i.e., from hypovolemia or low cardiac output) or renal tubular injury (e.g., from sepsis) (35). However, each of these measures has its limitations. (*Note:* Biomarkers are often mentioned for identifying renal tubular injury, but they are not readily available.)

Spot Urine Sodium

Renal hypoperfusion is accompanied by an increase in sodium reabsorption and a subsequent decrease in urine sodium concentration. In contrast, renal tubular injury results in impaired sodium reabsorption and increased urinary sodium losses. Therefore, when a random urine sample (spot urine) is obtained in a patient with AKI, a urine sodium <20 mEq/L is used as evidence of renal hypoperfusion, while a urine sodium >40 mEq/L is used as evidence of renal tubular injury.

EXCEPTIONS: Unfortunately, there are exceptions to the predicted behavior of the spot urine sodium. For example, renal hypoperfusion can be associated with a high urine sodium (>40 mEq/L) if there is ongoing diuretic therapy, or the patient has chronic renal disease (where there is "obligatory" sodium loss in the urine).

TABLE 34.4 Urinary Indices for the Evaluation of AKI

Measure	Renal Hypoperfusion	Renal Tubular Injury
Spot Urine Sodium	<20 mEq/L	>40 mEq/L
Fractional Excretion of Sodium	<1%	>12%
Fractional Excretion of Urea	<35%	>50%
Urine Osmolality	>500 mOsm/kg	300–400 mOsm/kg
U/P Osmolality	>1.5	1–1.3

Fractional Excretion of Sodium

The fractional excretion of sodium (FENa) is considered a more accurate measure of renal tubular function than the spot urine sodium. The FENa is equivalent to the fractional sodium clearance divided by the fractional creatinine clearance, as expressed by the following equation:

$$\text{FENa}\ (\%) = \frac{\text{U/P}\ [\text{Na}]}{\text{U/P}\ [\text{Cr}]} \tag{34.4}$$

where U/P is the urine-to-plasma ratio for sodium and creatinine concentrations. In euvolemic patients with normal renal function, the FENa is 1% (i.e., only 1% of the filtered sodium is excreted in the urine). When renal hypoperfusion is present, the FENa is <1% (reflecting sodium

conservation), and when renal tubular injury is present, the FENa is typically >2% (reflecting an increase in urinary sodium excretion) (36).

EXCEPTIONS: Like the spot urine sodium, the FENa can be elevated (>1%) by diuretic therapy and chronic renal insufficiency (36). In addition, the FENa can be falsely low (<1%) in patients with acute tubular injury from sepsis (37), or myoglobinuria (38).

Fractional Excretion of Urea

The fractional excretion of urea (FEU) is conceptually similar to the FENa, and is equivalent to the fractional urea clearance divided by the fractional creatinine clearance, as expressed by the following equation:

$$\text{FEU (\%)} = \frac{\text{U/P [Urea]}}{\text{U/P [Cr]}} \qquad (34.5)$$

U/P [Cr]

where U/P is the urine-to-plasma ratio for urea and creatinine concentrations. The FEU is low (<35%) with renal hypoperfusion, and high (>50%) with renal tubular injury. *The FEU is not influenced by diuretics* (39), which is the major advantage over the FENa.

MANAGEMENT

General Considerations

The following comments about the general management of AKI deserve mention.

Fluid Challenges

Volume infusion is typically the initial intervention in patients with AKI, since it is often not possible to rule out renal hypoperfusion as a contributing factor at that time, and the urine output may also be diminished. The fluid challenge is usually 500 mL of a crystalloid fluid infused over 10–15 minutes. (The rate of infusion is more important than the volume). Changes in stroke volume can be used to determine fluid responsiveness, as described in Chapter 11. Fluid challenges should be stopped if there is no response in the stroke volume or urine output.

Diuretics

A trial of intravenous furosemide is reasonable as an attempt to mitigate fluid accumulation in AKI. However, *diuretics should never be given to increase urine output if renal hypoperfusion is a contributing factor in AKI*. Intravenous furosemide does not improve renal function, and is used solely for fluid management (40,41).

Low-Dose Dopamine

Dopamine infusions at low dose rates (2 µg/kg/min) can promote renal vasodilation, which led to the popularity of low-dose dopamine as a treatment for AKI (42). However, this practice fell from favor because it did not improve renal function, and had undesirable effects (e.g., decreased

splanchnic blood flow) (42,43). The use of low-dose dopamine in AKI is now considered *bad medicine* (from the title of Reference 43).

Renal Replacement Therapy

About 10-15% of ICU patients receive renal replacement therapy (RRT) (4). The usual indications include: (a) symptomatic uremia (e.g., encephalopathy), (b) volume overload, (c) life-threatening, refractory hyperkalemia, and (c) removal of toxin (44).

There is a growing body of RRT techniques, but the descriptions that follow are limited to hemodialysis and hemofiltration. The mechanisms of fluid and solute removal by each of these techniques is shown in Figure 34.4.

Hemodialysis

Hemodialysis is an intermittent form of RRT that removes solutes by *diffusion*, which is driven by the concentration gradient of the solutes across a semipermeable membrane. To maintain this concentration gradient, a technique called *countercurrent exchange* is used, where blood and dialysis fluid are driven in opposite directions across the dialysis membrane. A blood pump is used to move blood in one direction at a rate of 200–300 mL/min, while the dialysis fluid on the other side of the membrane moves at a higher rate (500–800 mL/min) (37).

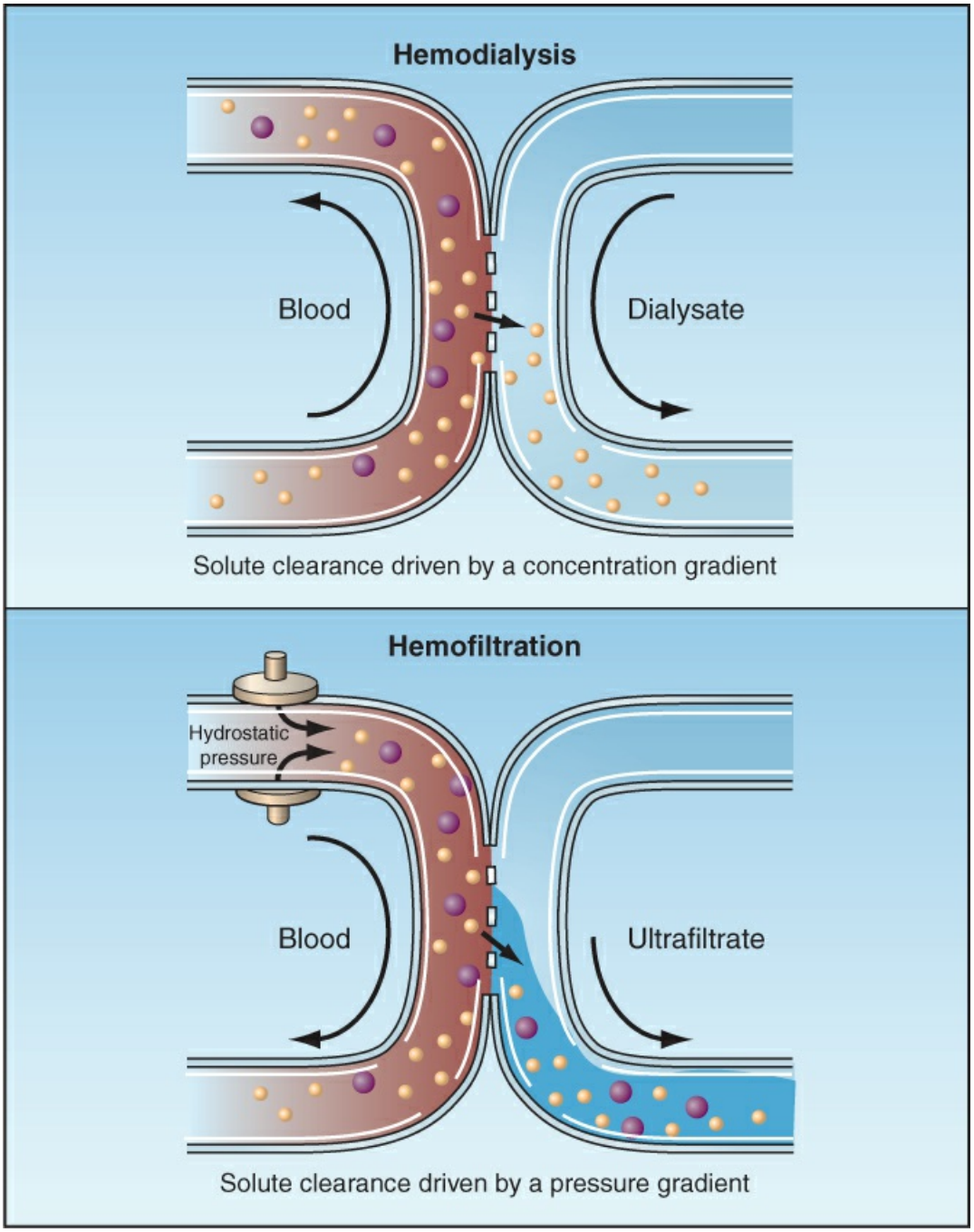

FIGURE 34.4 Mechanisms of solute clearance by hemodialysis and hemofiltration. The smaller particles represent small solutes (e.g., urea), which can be cleared by both techniques, while the larger particles represent larger solutes (e.g., toxins) that can be cleared by hemofiltration, but not by hemodialysis.

Large-bore, central venous catheters like the one in Figure 34.5 are used for acute hemodialysis in the ICU. Note that the catheter has 12-gauge infusion channels, to accommodate the flow rates of 200–300 mL/min used during hemodialysis. These catheters are inserted into the internal jugular or femoral veins in the same manner as other central venous catheters (see Chapter 2). (*Note:* The subclavian vein is not cannulated, which avoids the risk of subclavian

stenosis that could hamper the selection of access sites for long-term hemodialysis.) Each hemodialysis session lasts about 4 hours, and no more than 2–3 liters of fluid can be removed per session.

ADVANTAGES: The principal benefit of hemodialysis is rapid clearance of small solutes. Only a few hours of hemodialysis is needed to clear a life-threatening accumulation of potassium, or to remove a day's worth of accumulated nitrogenous waste.

DISADVANTAGES: The disadvantages of hemodialysis include: (a) limited removal of fluid and large molecules (drugs and toxins) and (b) the risk of hypotension in patients who are hemodynamically unstable.

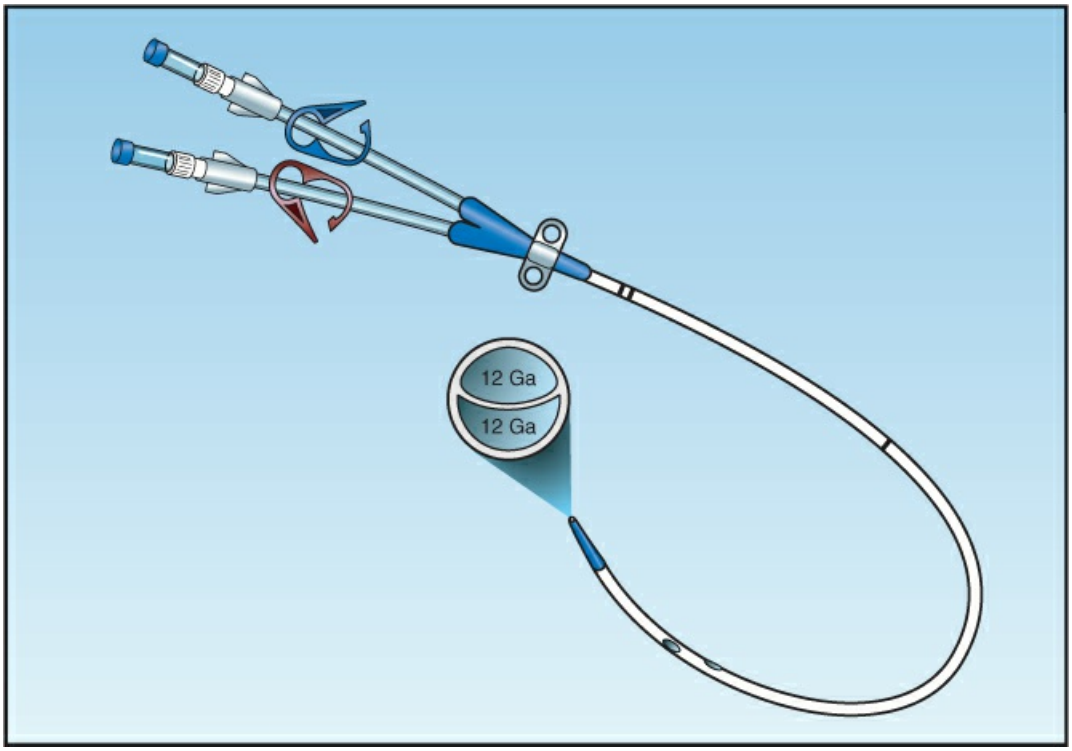

FIGURE 34.5 Central venous catheter for hemodialysis, which has two 12-gauge infusion channels, and is 20 cm (8 inches) in length.

Hemofiltration

Hemofiltration removes solutes by *convection*, where a hydrostatic pressure gradient is used to move a solute-containing fluid across a semipermeable membrane. The bulk movement of fluid "drags" the solute across the membrane, hence this process is also known as *solvent drag* (45).

Hemofiltration can remove large volumes of fluid (up to 3 liters per hour), but the rate of small solute clearance is much slower than during hemodialysis. As a result, *hemofiltration must be performed continuously to provide effective solute clearance*. The popular method is *continuous venovenous hemofiltration* (CVVH), where venous blood is removed and returned through large-bore, double-lumen catheters like the ones used for hemodialysis. Because solutes are cleared with water, the plasma concentration of these solutes does not decrease unless a

solute-free intravenous fluid is infused to replace some of the ultrafiltrate that is lost.

ADVANTAGES: The advantages of CVVH include: (*a*) improved tolerance in hemodynamically unstable patients, (*b*) ability to remove large volumes of fluid, and (*c*) ability to remove drugs and toxins. CVVH with increased pore size is also effective in removing inflammatory cytokines from blood (46), which has important implications for patients with sepsis and septic shock (where the organ dysfunction is inflammatory in origin).

DISADVANTAGES: The major disadvantage of hemofiltration is the slow removal of small solutes, which is not well suited for clearing nitrogenous waste or for life-threatening hyperkalemia.

Hemodiafiltration

Hemodiafiltration combines the benefits of dialysis (rapid clearance of small solutes) and hemofiltration (removal of fluid and toxins), and can be delivered as *continuous venovenous hemodiafiltration* (CVVHD). This has become the favored method of renal replacement therapy in the ICU, although the performance can be fickle.

A FINAL WORD

The Dirac Equation & Acute Kidney Injury

The author of the introductory quote (Paul Dirac) was a theoretical physicist who introduced an equation (the Dirac equation) to describe the behavior of all electrons (*a*). However, the equation ultimately failed in its intended task, which prompted the introductory quote. This has some similarities to the concept of acute kidney injury, which attempts to encompass the entire spectrum of acute renal dysfunction, but ultimately fails in its intended task. (For example, it fails to reliably identify renal dysfunction because it relies on the serum creatinine.) In fact, it is not entirely clear how the term “acute kidney injury” offers anything over the time-honored term “acute renal dysfunction”.

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Chapter 35

Sodium

People say life can't exist without air, but it does under water; in fact, it started in the sea.

Richard Feynman (*a*)

Life originated in a 3.5% salt water solution (i.e., the salinity of the ocean), and humans have retained some of that heritage, since our cells are bathed in a 0.6% salt water solution. The salinity (sodium concentration) of this extracellular bath is highly regulated, because it plays an important role in determining the volume of the intracellular and extracellular fluid compartments.

This chapter begins by describing the forces that determine the distribution of total body water, and the importance of sodium in determining these forces, and then presents an organized approach to the "dysnatremias" (1,2); i.e., hypernatremia and hyponatremia.

OSMOTIC ACTIVITY

The movement of water between fluid compartments is determined by a property of fluids known as *osmotic activity*, which is a reflection of the *number of solute particles* per unit volume of solvent (3). Osmotic activity is a *colligative property*, and depends only on the number of solute particles in a fluid, and not on the electrical charge, size, or chemical behavior of the solutes. The total osmotic activity of a solution is the summed osmotic activity of all the solute particles in the solution.

Relative Osmotic Activity

When two fluid compartments are separated by a membrane that is permeable to solutes and water, the solutes in each fluid compartment will equilibrate across the membrane, and the osmotic activity will be equivalent in both fluid compartments. Since water movement follows solute movement, the volume in both fluid compartments will be equivalent. This is illustrated in the Figure 35.1 (see the panel on the left).

Effective Osmotic Activity

When two fluid compartments are separated by a membrane that is not freely permeable to solutes, the solutes will not distribute evenly in the fluid compartments, and the osmotic activity will be different in each compartment. In this situation, water moves from the fluid with the lower osmotic activity (which has a higher water content) to the fluid with the higher osmotic activity (which has a lower water content), as demonstrated in the panel on the right in Figure 35.1. The difference in osmotic activity between the fluid compartments is called the *effective osmotic activity*, and it is the force that drives the movement of water between the fluid compartments. This force is also called the *osmotic pressure*.

The relative osmotic activity between two fluid compartments is expressed as *tonicity*; i.e., if the osmotic activity in the two compartments is equal, the fluids are described as *isotonic* (see the left-side panel in Figure 35.1), and if the osmotic activity differs, the fluid with the higher osmotic activity is described as *hypertonic*, and the fluid with the lower osmotic activity is described as *hypotonic* (see the right-side panel in Figure 35.1).

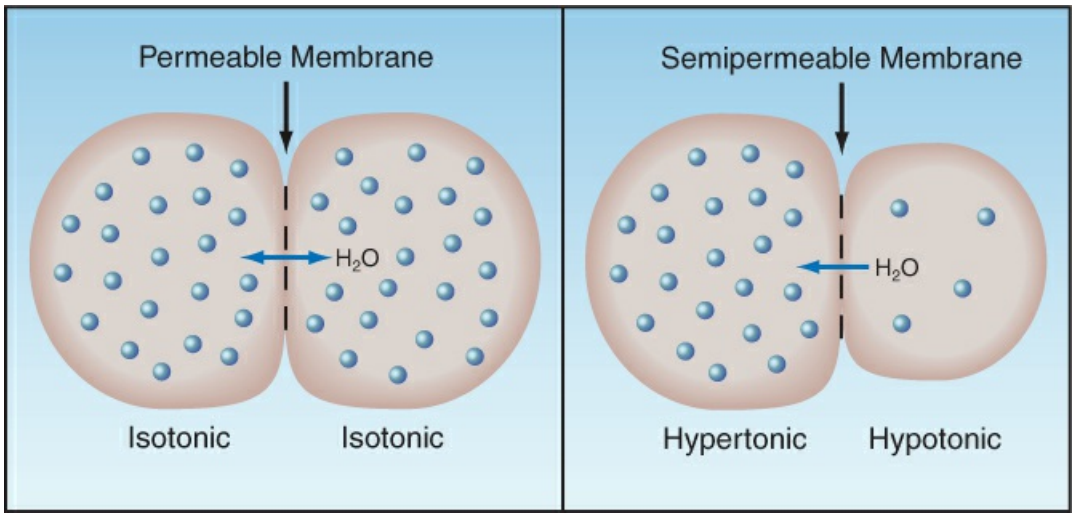

FIGURE 35.1 Illustration of the relationship between osmotic activity and water movement between fluid compartments. See text for explanation.

Summary

The following statements summarize the relationship between osmotic activity and the transcellular shift of water.

. A change in the effective osmotic activity or *tonicity* of extracellular fluid produces a transcellular water shift.

a. When the extracellular fluid is hypertonic, water moves out of cells.
b. When the extracellular fluid is hypotonic, water moves into cells.

Units of Osmotic Activity

The unit of measurement for osmotic activity is the osmole (osm), which is defined as one gram molecular weight (one mole) of a nondissociable substance, and is equivalent to 6×10^{23} particles (Avogadro's Number). Osmotic activity can be expressed in relation to the volume of water in a solution, or in relation to the volume of the solution (4,5).

. Osmotic activity per volume of solution is called *osmolarity*, and is expressed as milliosmoles per liter (mosm/L).

. Osmotic activity per volume of water is called *osmolality*, and is expressed as milliosmoles per kilogram of H_2O (mosm/kg H_2O, or mosm/kg).

Plasma is mostly (95%) water, so the osmotic activity in plasma is typically expressed as osmolality (mosm/kg H_2O). However, there is little difference between the osmolality and osmolarity of extracellular fluid, and the two terms are often used interchangeably (5).

Conversion Factors

The following formulas (where n is the number of nondissociable particles) can be used to convert plasma solute concentrations to units of osmolality:

. For solute concentrations expressed in mEq/L:

$$\frac{\text{mEq/L}}{\text{valence}} \times \text{n} = \text{mosm/kg } H_2O \tag{35.1}$$

Thus, for univalent ions like sodium, the plasma concentration in mEq/L is equivalent to the osmotic activity in mosm/kg H_2O.

. For solute concentrations expressed in mg/dL:

$$\frac{\text{mg/dL} \times 10}{\text{mol wt}} \times \text{n} = \text{mosm/kg } H_2O \tag{35.2}$$

where mol wt is molecular weight, and the factor 10 is used to convert deciliters (dL) to liters. For example, glucose has a molecular weight of 180, so a plasma glucose concentration of 90 mg/dL is equivalent to (90 × 10/180) × 1 = 5 mosm/kg H_2O.

Plasma Osmolality

The plasma osmolality can be measured or calculated.

Measured Plasma Osmolality

The standard method for measuring plasma osmolality is the *freezing point depression* method. Solute-free water freezes at 0º C, and this temperature decreases by 1.86° C for each osmole of solute that is added to one kilogram of water. Therefore, the extent of depression of the freezing point of an aqueous solution can be used to determine the osmotic activity of the solution. This method is considered the “gold-standard” for measuring plasma osmolality, and is available in most clinical laboratories. The normal plasma osmolality is 285–295 mosm/kg H_2O.

Calculated Plasma Osmolality

Plasma osmolality can also be calculated using the concentrations of the principal solutes in plasma; i.e., sodium, chloride, glucose, and urea (3); i.e.,

$$\text{Posm} = 2 \times \text{Na} + \frac{\text{glucose}}{18} + \frac{\text{BUN}}{2.8} \quad (35.3)$$

where Posm is the plasma osmolality in mosm/kg H_2O, Na is the plasma sodium concentration in mEq/L, glucose and BUN are the plasma glucose and urea concentrations in mg/dL, and the factors 18 and 2.8 are the molecular weights of glucose and urea divided by 10, respectively (which converts their concentrations to mosm/kg H_2O). The sodium concentration is doubled to account for the negative ions (mostly chloride) that electrically balance sodium.

EXAMPLE: Using normal plasma concentrations of Na (140 mEq/L), glucose (90 mg/dL), and BUN (14 mg/dL), the plasma osmolality is: (2 × 140) + 90/18 + 14/2.8 = 290 mosm/kg H_2O. This is within the range of the measured plasma osmolality (285–295 mosm/kg H_2O).

EFFECTIVE PLASMA OSMOLALITY: Urea readily crosses cell membranes, so an increase in blood urea nitrogen (BUN) will not increase the effective osmotic activity of plasma. In other words, *azotemia is a hyperosmotic, but not a hypertonic, condition*. Therefore, the calculation of effective plasma osmolality does not include the BUN; i.e.,

$$\text{Effective Posm} = (2 \times \text{Na}) + \frac{\text{glucose}}{18} \quad (35.4)$$

EXAMPLE: Using normal plasma concentrations of Na (140 mEq/L) and glucose (90 mg/dL), the effective plasma osmolality is (2 × 140) + 90/18 = 285 mosm/kg H_2O, which is very close to the total osmolality (290 mosm/kg H_2O).

Spotlight on Sodium

If the glucose is removed from Equation 35.4, the calculated Posm is 280 mosm/kg H_2O, which is 98% of the calculated Posm that includes glucose (i.e., 285 mosm/kg H_2O). This demonstrates the following:

. Sodium is responsible for 98% of the effective plasma osmolality.

. The sodium concentration in extracellular fluid (plasma) is the principal factor that determines the distribution of total body water in the intracellular and extracellular fluid compartments, and hence it is also the principal determinant of the extracellular volume.

HYPERNATREMIA

Hypernatremia (i.e., plasma sodium >145 mEq/L) has been reported in as many as 25% of ICU patients, and *in most cases, it is acquired during the ICU stay* (6). The mechanisms and management of hypernatremia are outlined in Figure 35.2. This approach is based on the extracellular volume (ECV), and this creates three categories of hypernatremia: hypovolemic, normovolemic, and hypervolemic.

Hypovolemic Hypernatremia

Hypernatremia associated with a low ECV is due to fluid loss that is hypotonic to plasma. The average sodium concentration in fluids that can be lost is shown in Table 35.1 (7–9). Note the following:

. All the fluids are hypotonic to plasma (i.e., have a sodium concentration <135 mEq/L), so loss of these fluids will in hypernatremia.

. All the fluids contain sodium, so loss of these fluids will result in sodium depletion as well as water depletion.

Common sources of hypotonic fluid loss in ICU patients include vomiting, diarrhea, and urine loss from diuretics or glycosuria.

Consequences

Hypernatremia increases the osmolality of the extracellular fluid, which draws water out of cells and decreases cell volumes. This effect is most prominent in the brain. However, the shrunken brain cells begin to regain volume after about 9 hours, thanks to the intracellular accumulation of "idiogenic osmolytes", and the cells can return to their normal volumes after just 48 hours (10).

TABLE 35.1 Average Sodium Concentration in Select Fluids

Normal	Na (mEq/L)	Other	Na (mEq/L)
Gastric Secretions	60	Diuretic Urine	80
Stool	25	Ileostomy Drainage	125
Urine	<10	Inflammatory Diarrhea	75
Sweat	65	Secretory Diarrhea	90

From References 7–9.

HYPERNATREMIC ENCEPHALOPATHY: The most common complication of hypernatremia is an encephalopathy that varies widely in incidence and severity. It is more likely to appear when the rise in serum sodium is rapid, and can present with lethargy, cognitive impairment, delirium, seizures and even coma (6,11). Cell shrinkage and osmotic demyelination are recognized as the culprits (11).

OTHERS: Hypernatremia has surprisingly few adverse consequences other than the encephalopathy. There are occasional reports of rhabdomyolysis (12), which often appears along with the encephalopathy (11). Hypertonicity also has negative inotropic effects, but there is no evidence that this results in heart failure. Finally, hypotonic fluid loss does not decrease the blood pressure unless fluid losses are severe, because the loss of hypotonic fluids increases the osmotic pressure in plasma, which draws fluid from the interstitial space into the plasma to help maintain intravascular volume.

Management

Isotonic saline is used to correct hypotension, but not to correct the hypernatremia (because it is

ineffective) (13). The recommended fluid regimens to correct the hypernatremia include the infusion of 5% dextrose in water (D_5W), or the addition of water to enteral tube feedings (e.g., 200 mL every 8 hours) (6,13). However, hypotonic fluid loss also results in the loss of sodium, so 0.45% (half-normal) saline seems more appropriate than D_5W as a replacement fluid.

RATE OF CORRECTION: Aggressive infusion of hypotonic fluids has always been discouraged because of the risk of cerebral edema, which is heightened by the accumulation of osmolytes in shrunken brain cells that helps regain the original cell volume. The optimal correction rate for hypernatremia is not known, but the traditional recommendation has been to limit the rate of correction to ≤0.5 mEq/L/hr (2,14). However, correction rates exceeding 0.5 mEq/L/hr have been used safely, without causing cerebral edema (14).

Normovolemic Hypernatremia

Hypernatremia in the setting of a normal ECV is usually the result of water loss without significant sodium loss. This condition is common in ICU patients with hypernatremia (15), and occurs when the replacement fluid is hypertonic to the fluid that is lost. (With this scenario, sodium losses are replaced, but a net water deficit remains.) Selective loss of free water is also characteristic of diabetes insipidus.

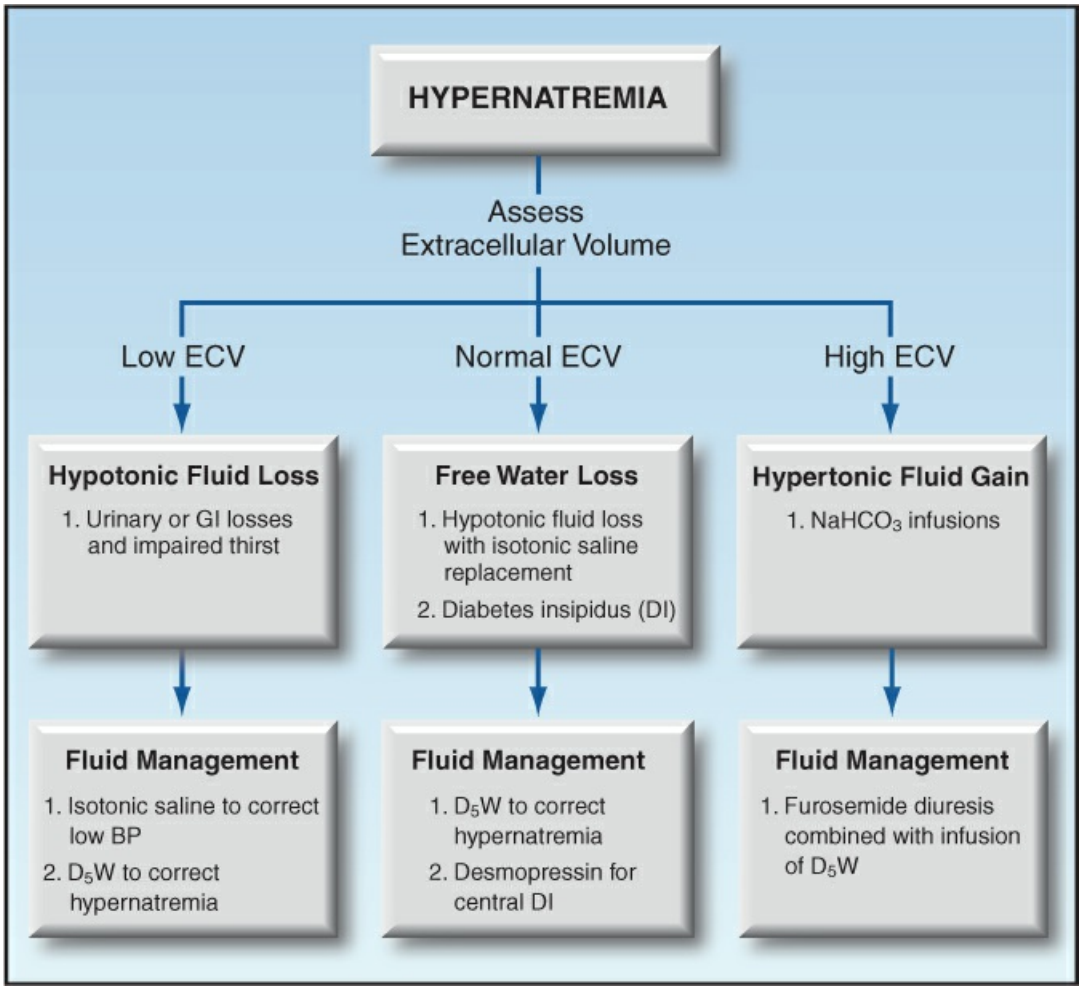

FIGURE 35.2 Flow diagram for hypernatremia based on the extracellular volume (ECV).

Diabetes Insipidus

Diabetes insipidus (DI), is a disorder of renal water conservation, and is characterized by loss of urine that is largely devoid of solute (16,17). The underlying problem in DI is loss of the effect produced by the antidiuretic hormone (ADH), a polypeptide released by the posterior pituitary gland that promotes water reabsorption in the distal renal tubules. Three types of DI are recognized:

. *Central DI* is characterized by failure of ADH release from the posterior pituitary (16). Common causes include surgical resection of a pituitary tumor, traumatic brain injury, subarachnoid hemorrhage, and autoimmune diseases (16).

. *Nephrogenic DI* is characterized by impaired renal responsiveness to ADH. Possible causes in critically ill patients include drugs (amphotericin, aminoglycosides, dopamine, lithium, etc.), hypokalemia, and the recovery phase of ATN (17).

. *Gestational DI* is the result of a vasopressinase enzyme that is produced by the placenta and inactivates arginine vasopressin (ADH) (18). Production of the enzyme increases throughout pregnancy, and the DI usually appears at the end of the second, or in the third, trimester.

DIAGNOSIS: The hallmark of DI is a dilute urine in the face of hypertonic plasma. In central DI, the urine osmolarity is often below 200 mosm/L, whereas in nephrogenic DI, the urine osmolarity is 200–500 mosm/L (19). The diagnosis of DI is based on the response of the urine osmolality to fluid restriction. Failure of the urine osmolarity to increase more than 30 mosm/L in the first few hours of complete fluid restriction will identify a case of DI. The response to vasopressin can then differentiate central from nephrogenic DI; i.e., in central DI, the urine osmolality increases by at least 50% after vasopressin administration, whereas in nephrogenic DI, the urine osmolality is unchanged after vasopressin.

DESMOPRESSIN: In central DI, renal water retention can be restored with the administration of *desmopressin*, a synthetic analog of vasopressin that lasts longer, and has no vasoconstrictor effects. Desmopressin is available as an oral tablet, an intranasal spray, and a parenteral preparation for subcutaneous or intravenous injection. Only 5% of the drug is absorbed from the GI tract (20), so the oral route is least desirable. The parenteral dose of desmopressin is 1 μg by subcutaneous injection every 12 hours, or 2 μg by IV injection every 12 hours (20).

NSAIDS: The approach to nephrogenic DI involves removing any offending drug, but this does not always correct the problem. When this occurs, nonsteroidal anti-inflammatory drugs (NSAIDs) can increase renal responsiveness to ADH (because prostaglandins block the actions of ADH, and NSAIDs inhibit prostaglandin synthesis). Indomethacin (2 mg/kg/day) has been more successful than other NSAIDs in restoring ADH responsiveness (21).

Hypervolemic Hypernatremia

Hypernatremia with a high extracellular volume can be the result of sodium bicarbonate infusions, but it is more frequently associated with excessive infusions of isotonic saline for

hypotonic fluid loss.

Management

In patients with normal renal function, excess sodium and water are excreted rapidly. When renal sodium excretion is impaired, it might be necessary to increase renal sodium excretion with a diuretic (e.g., furosemide). Because the urinary sodium concentration during furosemide diuresis (~80 mEq/L) is less than the plasma sodium concentration, diuresis can aggravate the hypernatremia. Therefore, the diuresis should be combined with infusions of D_5W to correct the hypernatremia.

HYPONATREMIA

Hyponatremia (plasma [Na] < 135 mEq/L) is considered the most common electrolyte abnormality in clinical practice (22), and is found in 30–40% of hospitalized patients (23).

Pseudohyponatremia

Plasma has an aqueous phase and a solid (nonaqueous) phase. Small electrolytes like sodium are confined to the aqueous phase, while larger molecules like lipids and proteins are located in the solid phase. The automated measurements performed in the clinical laboratory include both phases of plasma (24), and thus the measured plasma sodium could underestimate the actual (aqueous phase) sodium level. However, 95% of the plasma is water (i.e., aqueous phase), so there is normally little difference between the measured and actual sodium concentrations.

However, a problem arises when there is a marked increase in protein or lipid levels in blood. In this situation, there is an increase in the nonaqueous or solid phase of plasma, which will decrease the measured plasma sodium concentration, while the actual (aqueous phase) sodium concentration is unchanged. This spurious decrease in the measured plasma sodium is called *pseudohyponatremia* (24), and it becomes significant when plasma protein levels reach 12 g/dL (normal range is 5.5–8 g/dL), and triglyceride levels rise to 1,500 mg/dL (normal range is 25–175 mg/dL). The clinical conditions that can produce pseudohyponatremia are listed in Table 35.2 (24).

TABLE 35.2 Clinical Conditions Associated with Pseudohyponatremia

Mechanism	Conditions
Hyperproteinemia	HIV Disease Immunoglobulin Infusions Monoclonal Gammopathies Multiple Myeloma Waldenström's Macroglobulinemia
Hypertriglyceridemia	Alcohol Abuse Diabetic Ketoacidosis Hyperlipidemias (types I and V) Pancreatitis Type 2 Diabetes (poorly controlled)

Hypercholesterolemia	Biliary Obstruction Hepatitis Intrahepatic Cholestasis Primary Biliary Cirrhosis

From Reference 24.

Diagnosis

Pseudohyponatremia can be uncovered by measuring the plasma osmolality, which will be normal (285–295 mosm/kg H_2O) with pseudohyponatremia, and will be reduced (<275 mosm/kg H_2O) with true hyponatremia.

Hyperglycemia

Hyperglycemia is another potential cause of spurious hyponatremia. When glucose does not readily enter cells, the resultant hyperglycemia draws fluid out of cells. This increases the aqueous phase of plasma, and has a dilutional effect on sodium. For every 100 mg/dL increase in blood glucose, there is a 2.4 mEq/L decrease in the serum sodium concentration (22,25). This is expressed in the following equation:

$$\text{Corrected [Na]} = \text{Measured [Na]} + \left[2.4 \times \frac{\text{glucose} - 100\ (\text{mg/dL})}{100\ (\text{mg/dL})} \right] \quad (35.5)$$

EXAMPLE: If a patient with a serum sodium concentration of 130 mEq/L also has a blood glucose of 600 mg/dL, the corrected serum sodium is 130 + (2.4 × 5) = 142 mEq/L.

The Approach

The evaluation and management of true hyponatremia can be organized around the extracellular volume (ECV), as shown in Figure 35.3. This approach is similar to the one used for hypernatremia, and it has three types of hyponatremia: hypovolemic, normovolemic, and hypervolemic.

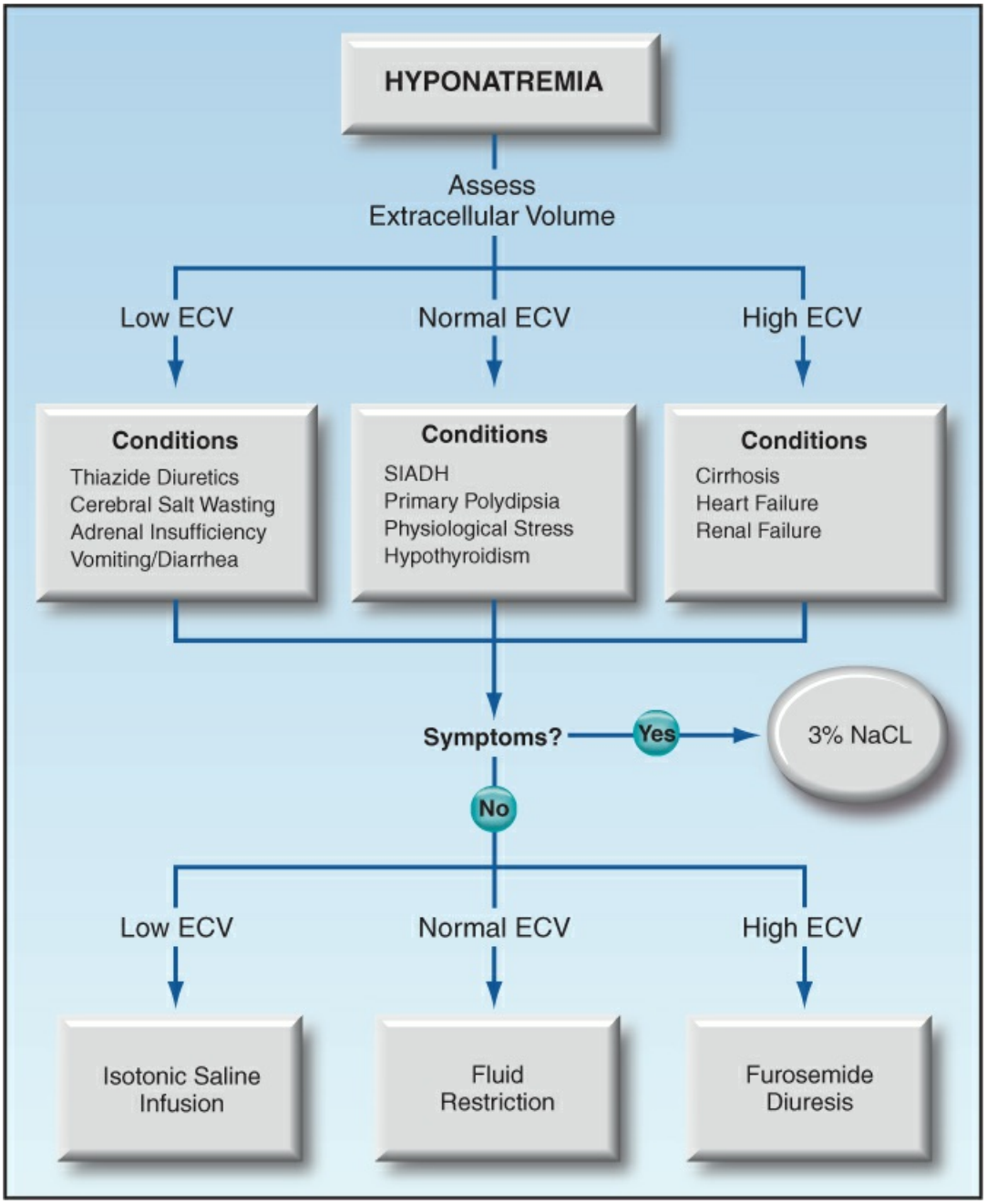

FIGURE 35.3 Flow diagram for hyponatremia based on the extracellular volume (ECV).

Hypovolemic Hyponatremia

Hyponatremia with a low ECV is the result of sodium loss in the urine or GI tract, combined with impaired water excretion by the kidneys (26). Water retention is needed to produce the hyponatremia (because loss of hypotonic fluids results in *hyper*natremia), and is the result of the following events: (*a*) the sodium losses result in hypovolemia, which stimulates the renin-angiotensin-aldosterone system, (*b*) the released angiotensin stimulates the release of antidiuretic hormone (ADH) from the posterior pituitary gland, and (*c*) ADH promotes water retention by the kidneys.

Etiologies

The clinical conditions that promote hypovolemic hyponatremia are listed in Figure 35.3. The most cited causes are thiazide diuretics, adrenal insufficiency, and cerebral salt wasting.

THIAZIDE DIURETICS: Hypernatremia is reported in about one-third of patients being treated with a thiazide diuretic, and usually appears after 3 weeks of treatment (27). The mechanism for the hyponatremia is complex, and beyond the intent of this chapter.

ADRENAL INSUFFICIENCY: Primary adrenal insufficiency involves mineralocorticoid deficiency, which promotes renal sodium wasting. The hyponatremia usually appears in the chronic (not acute) form of illness. Secondary adrenal insufficiency (which originates in the hypothalamus or pituitary) is primarily a deficiency of glucocorticoids, and is not associated with hyponatremia.

CEREBRAL SALT WASTING: Cerebral salt wasting is a condition of urinary sodium loss and hyponatremia that is associated with neurologic disorders, especially subarachnoid hemorrhage, traumatic brain injury, CNS infections, Guillain-Barre Syndrome, and neurosurgery (28).

Diagnostic Considerations

The source of sodium loss (i.e., kidneys or GI tract) is usually apparent, but if not, a spot urine sodium can help to distinguish renal from extrarenal losses; i.e., urine $Na^+ > 20$ mEq/L suggests a renal source of sodium loss, while a urine $Na^+ < 20$ mEq/L suggests an extrarenal site of sodium loss.

Normovolemic Hyponatremia

Hyponatremia with a normal ECV is the result of water retention with minimal sodium loss. This is usually the result of uncontrolled, “nonosmotic” release of ADH from the pituitary, or excessive water intake.

Etiologies

This causes of normovolemic hyponatremia include: the syndrome of inappropriate ADH (SIADH), primary polydipsia, physiological stress, and (rarely) hypothyroidism (see Figure 35.3).

SIADH: SIADH is a condition of uncontrolled or nonosmotic release of ADH that is associated with a variety of other conditions, including neoplasms, infections, and drugs. The hallmark of SIADH is the combination of hypotonic plasma, inappropriately concentrated urine (urine osmolality >100 mosm/kg H_2O) and an elevated urine sodium (>20 mEq/L) (29). This condition can be difficult to distinguish from cerebral salt wasting, and the only difference may be the ECV (which is decreased with cerebral salt wasting, and normal with SIADH).

PHYSIOLOGICAL STRESS: Physiological stress is well known for promoting the release of ACTH from the anterior pituitary, but a lesser known component of the stress response is the release of ADH from the posterior pituitary. (Teleologically, water retention from the actions of ADH should be advantageous during periods of stress, when insensible losses are likely to be high.)

Stress-induced release of ADH would explain the increased risk of hyponatremia in postoperative patients (22), and this should also apply to critically ill patients. The popularity of hypotonic IV fluids like Ringer's lactate adds further to the risk of hyponatremia in hospitalized patients (30). (See Table 10.2 for the osmolarity of intravenous fluids.)

PRIMARY POLYDIPSIA: Water intoxication (primary polydipsia) is a source of hyponatremia that occurs primarily in patients with developmental or psychiatric disorders (31). Patients with hyponatremia from polydipsia also have impaired free water clearance by the kidneys (32), and both factors may be necessary to produce sustained hyponatremia.

Another example of hyponatremia caused by heavy consumption of a dilute fluid is *beer potomania* (33), which is typically found in chronic alcoholics who are poorly nourished and are prone to binge drinking.

HYPOTHYROIDISM: Although hypothyroidism is considered a cause of hyponatremia, the evidence for this is not convincing. For example, a retrospective analysis of 8,000 patients with hypothyroidism revealed that 5% of the patients had hyponatremia, but almost all (98%) of these patients had other conditions that could have caused the hyponatremia (34). Despite the difficulty establishing a causal link between hypothyroidism and hyponatremia, a serum TSH assay is recommended in the evaluation of hyponatremia of undetermined etiology (34).

Diagnostic Considerations

When the cause of normovolemic hyponatremia is unclear, the urine osmolality can help to distinguish between SIADH and primary polydipsia: i.e., in SIADH, the unregulated actions of ADH produce a concentrated urine (urine osmolality 300–500 mosm/kg H_2O), whereas water intoxication produces a dilute urine (i.e., urine osmolality <200 mosm/kg H_2O).

Hypervolemic Hyponatremia

Hypervolemic hyponatremia is the result of salt and water retention, with water retention exceeding sodium retention. This condition occurs in advanced heart failure, cirrhosis, and renal failure. Renal failure is associated with a high urine [Na^+] (>20 mEq/L), while the urine [Na^+] is low (<20 mEq/L) in heart failure and cirrhosis (except when a diuretic is active).

MANAGEMENT OF HYPONATREMIA

The management of hyponatremia is determined by two factors: the ECV, and the presence or absence of hyponatremic encephalopathy.

Hyponatremic Encephalopathy

Hyponatremia results in a hypotonic extracellular fluid, which then causes fluid to move across the blood-brain barrier and into brain parenchyma. This process culminates in diffuse cerebral edema with an increased intracranial pressure (35), and when this condition produces symptoms, it is called *hyponatremic encephalopathy* (36). This is considered an immediate threat to life, and thus requires prompt action to reduce the cerebral edema with hypertonic saline.

Hyponatremic encephalopathy is more likely appear when the hyponatremia is acute (i.e., develops in less than 48 hours), but there is no correlation between the severity of the hyponatremia and the appearance or severity of the encephalopathy (36). As a result, *the plasma Na^+ concentration has no role in the decision about initiating hypertonic saline*.

Symptoms

Hyponatremic encephalopathy can present with a wide variety of symptoms, but the earliest symptoms usually include nausea, vomiting, headache, and ataxia, while advanced symptoms can include agitation, confusion, seizures, and coma. Although the early symptoms can be nonspecific, *the presence of any symptom that suggests possible cerebral edema is an indication for rapid correction of the hyponatremia with hypertonic saline*.

Hypertonic (3%) Saline

The treatment of symptomatic hyponatremia with hypertonic saline is summarized in Table 35.3. A 3% NaCL solution (Na^+ = 513 mEq/L, osmolarity = 1,026 mosm/L) is given in bolus doses of 2 mL/kg (or 150 mL), which are repeated every few hours until the symptoms resolve. Each bolus dose can increase the sodium concentration by as much as 2 mEq/L, and an increase of 5–6 mEq/L should produce some improvement in symptoms. If there is no improvement at this point, it is possible that hyponatremia is not the cause of the symptoms.

The 3% NaCL solution can be delivered safely through a peripheral vein (36,37), and treatment continues until the symptoms resolve. However, there are limits placed on the rate and extent of Na correction, as explained next.

TABLE 35.3 Hypertonic Saline for Symptomatic Hyponatremia

1. Use 3% NaCL (Na^+ = 153 mEq/L, osmolarity = 1,026 mosm/L).
2. Give IV bolus doses of 2 mL/kg (or 150 mL), which are repeated every few hours until the symptoms resolve. This regimen can be given via peripheral veins.
3. Assess after the serum Na^+ has increased by 5 mEq/L – if there is no improvement, consider another cause for the symptoms.
4. The following limits are recommended as a preventive measure for osmotic demyelination.
   a. The initial increment in serum Na^+ should not exceed 5 mEq/L in 2 hrs, or 10 mEq/L in 5 hrs.
   b. The daily increment in serum Na^+ should not exceed 10 mEq/L on the first day, and 8 mEq/L on subsequent days.
   c. The final plasma Na^+ should not exceed 130 mEq/L.

From References 22 and 36.

Osmotic Demyelination Syndrome

Correction of the sodium that is too rapid, or overshoots the normal sodium concentration can produce a devastating neurologic disorder caused by osmotic damage to the myelin sheath of brainstem neurons. This *osmotic demyelinating syndrome*, also known as ”central pontine myelinolysis”, has a biphasic course. The initial presentation includes varying degrees of altered mentation, along with seizures, but this improves, only to be followed at a later time by profound deterioration in overall health, with dysarthria, oculomotor dysfunction, quadriparesis, and even

locked-in syndrome. (38). Chronic hyponatremia poses a greater risk for this complication than acute (within 48 hrs) hyponatremia.

To reduce the risk of osmotic demyelination, the maximum rate of correction for Na^+ is limited to 8–10 mEq/L over any 24-hour period, and the end-point of Na^+ correction is a serum concentration of 130 mEq/L. (22,36). This end-point is below the normal range, but it provides a buffer against overshooting the end-point.

Overcorrection

Overcorrection of the serum sodium occurs in as many as 25% of cases (39), even when preventive measures are used. The tendency for overcorrection can be attributed to a spontaneous water diuresis that occurs in some patients during treatment with hypertonic saline. This diuresis decreases the extracellular volume, which concentrates the sodium and augments its rate of correction.

The water diuresis is more frequent in hyponatremia caused by drugs (especially thiazides) and by water intoxication. This diuresis can be prevented or terminated by desmopressin.

DESMOPRESSIN: Desmopressin (a synthetic analog of vasopressin) can be used as shown in Table 35.4 (40,41). It should be started when there is an abrupt increase in urine flow (indicating water diuresis) during corrective therapy with hypertonic saline, and it can be used routinely in cases of hyponatremia that have a high risk of overcorrection (i.e., hyponatremia from adrenal insufficiency, drugs, and primary polydipsia.) Fluid restriction is mandatory during therapy with desmopressin, to prevent the development of severe hyponatremia.

TABLE 35.4 Desmopressin to Prevent or Reverse Overcorrection of Hyponatremia

Indications: • If the increment in serum Na^+ exceeds the limits listed in Table 35.3. • If there is an abrupt increase in urine output (e.g., >100 mL/hr) during corrective therapy with hypertonic saline • As a routine measure in conditions where overcorrection is a risk (see text).
Dose: • 2 µg by subcutaneous injection every 12 hrs.
Caveats: • Desmopressin is not advised when the hyponatremia is due to unregulated release of ADH. • Fluid restriction is mandatory during R_x with desmopressin.

Asymptomatic Hyponatremia

Rapid correction of the hyponatremia is not necessary in asymptomatic patients. Instead, the fluid management is based on the ECV, as shown in Figure 35.3.

Hypovolemia

In cases of hypovolemic hyponatremia, isotonic saline will help to improve blood pressure and tissue perfusion, but the hyponatremia may not show significant improvement until the

responsible conditions are treated or eliminated.

Normovolemia

The problem in normovolemic hyponatremia is water excess without sodium excess, so fluid restriction is indicated. The usual goal is a daily fluid intake that is 500 mL less than the daily urine output (26). Fluid restriction is notoriously intolerable for patients, but the following drug options available for patients with SIADH.

DEMECLOCYCLINE: Demeclocycline is a tetracycline derivative that blocks the effects of ADH in the renal tubules. It is intended for patients with chronic SIADH who do not tolerate fluid restriction, and is given in a dose of 600–1,200 mg daily in divided doses (26). Maximum effect takes several days, and success is variable. Demeclocycline can be nephrotoxic, so monitoring renal function is advised while using the drug.

THE VAPTANS: The vaptans are vasopressin antagonists that block the actions of vasopressin (ADH) in the kidneys and elsewhere. There are two drugs in this class: conivaptan and tolvaptan. Conivaptan can be given intravenously, while tolvaptan is an oral medication. Both agents can increase the serum sodium by 6 or 7 mEq/L (42,43). These drugs are expensive and are not currently popular.

Hypervolemia

Patients with hypervolemic hyponatremia are both salt and water overloaded, with the water overload exceeding the salt overload. Furosemide diuresis could theoretically correct this problem. However, continued activation of the renin-angiotensin-aldosterone system in heart failure and cirrhosis helps to maintain the hyponatremia.

A FINAL WORD

What You See is Not What You Get

The fundamental truth about hypernatremia and hyponatremia is that they are disorders of water balance, not sodium balance. This “sleight of hand” is unique among electrolyte disorders; e.g., hypomagnesemia is a sign of magnesium depletion, but hyponatremia is a sign of water overload (absolute or relative), not sodium depletion. Understanding this basic distinction may help you to navigate through the maze of possibilities when confronting a patient with hypernatremia or hyponatremia.

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Chapter 36

Potassium

No knowledge can be more satisfactory to a man than that of his own frame, its parts, their functions and actions.

Thomas Jefferson (*a*)

The last chapter introduced the notion that the ocean served as extracellular fluid for the first unicellular organisms. Seawater is essentially a saline solution that is rich in sodium and chloride, and "poor" in potassium, similar to our extracellular fluid. Why there is so little potassium in seawater is not entirely explained, but the paucity of potassium in our extracellular fluid is the consequence of a membrane pump that keeps potassium in cells. About 98% of the total body potassium is located inside cells, and only 2% remains in the extracellular fluid (1–3). As a result, monitoring the plasma (extracellular) potassium level as an index of total body potassium is like evaluating an iceberg by its tip. With this limitation in mind, this chapter describes the causes and consequences of abnormalities in the plasma potassium concentration.

POTASSIUM BASICS

Potassium Distribution

The intracellular preponderance of potassium is the result of a sodium–potassium (Na^+–K^+) exchange pump on cell membranes that moves Na^+ out of cells and moves K^+ into cells in a 3:2 ratio (1). One of the major roles of this pump is to create a voltage gradient across cell membranes in "excitable" tissues (i.e., nerves and muscle), which allows for the transmission of electrical impulses in these tissues.

The marked difference between intracellular and extracellular K^+ is illustrated in Figure 36.1. The total body potassium in healthy adults is about 50–55 mEq per kg body weight (1). Using the conservative estimate of 50 mg/kg in a 70 kg adult yields a total body potassium of 3,500 mEq, with 70 mEq (2%) in extracellular fluid. Because the plasma accounts for about 20% of the extracellular fluid, the *potassium content of plasma* will be about 15 mEq, which *is only 0.4% of the total body potassium*. This emphasizes the limited size of the K^+ pool that is available for evaluating total body K^+.

Serum Potassium

The relationship between total body K^+ and serum (plasma) K^+ is shown in Figure 36.2 (4,5). Note the curvilinear shape of the curve, with the flat portion of the curve in the region of potassium deficiency. In an average-sized adult with a normal serum K^+ of 4 mEq/L, a total body K^+ deficit of 200–400 mEq is required to produce a decrease in plasma K^+ of 1 mEq/L, while a total body K^+ excess of 100–200 mEq is required to produce a similar (1 mEq/L) increase in plasma K^+ (5). Therefore, *for a given change in serum K^+, the change in total body K^+ is twofold greater with K^+ depletion (hypokalemia) than with K^+ excess (hyperkalemia)*. The larger K^+ deficit associated with hypokalemia is due to the large pool of intracellular K^+ that can replenish extracellular K^+ (and help to maintain serum K^+) when K^+ is lost.

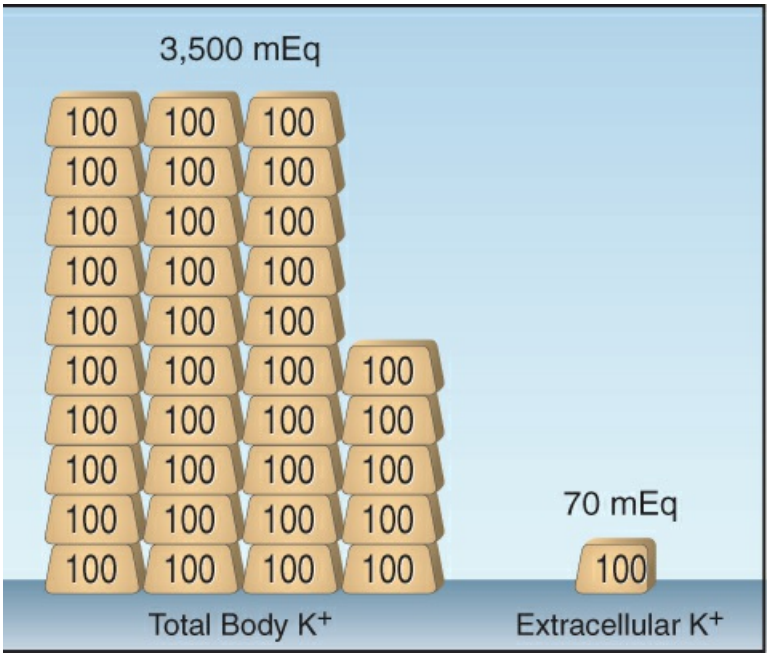

FIGURE 36.1 IIllustration of the marked difference between intracellular and extracellular potassium in a 70 kg adult with an estimated total body potassium of 50 mEq/kg. Each gold bar represents 100 mEq of potassium.

Potassium Excretion

Small amounts of K^+ are lost in stool (5–10 mEq/day) and sweat (0–10 mEq/day), but the majority of K^+ loss is in urine (40–120 mEq/day, depending on K^+ intake) (1).

Renal Excretion

Most of the K^+ that is filtered at the glomerulus is passively reabsorbed in the proximal tubules (along with sodium and water), and K^+ is then secreted in the distal tubules and collecting ducts (1). Potassium excretion in urine is primarily a function of K^+ secretion in the distal nephron, which is controlled by plasma K^+ and (primarily by) aldosterone. When renal function is normal, the capacity for renal K^+ excretion is great enough to prevent a sustained rise in serum K^+ in response to an increased K^+ load (1).

ALDOSTERONE: Aldosterone is a mineralocorticoid that is released by the adrenal cortex in

response to an increase in plasma K^+ (and angiotensin II), and it stimulates K^+ secretion in the distal nephron (and hence increases urinary K^+ excretion). Potassium secretion in the distal nephron is linked to sodium reabsorption, so aldosterone also promotes sodium and water retention. The diuretic *spironolactone* acts by blocking the actions of aldosterone in the kidneys. As a result, spironolactone is a *potassium-sparing diuretic*.

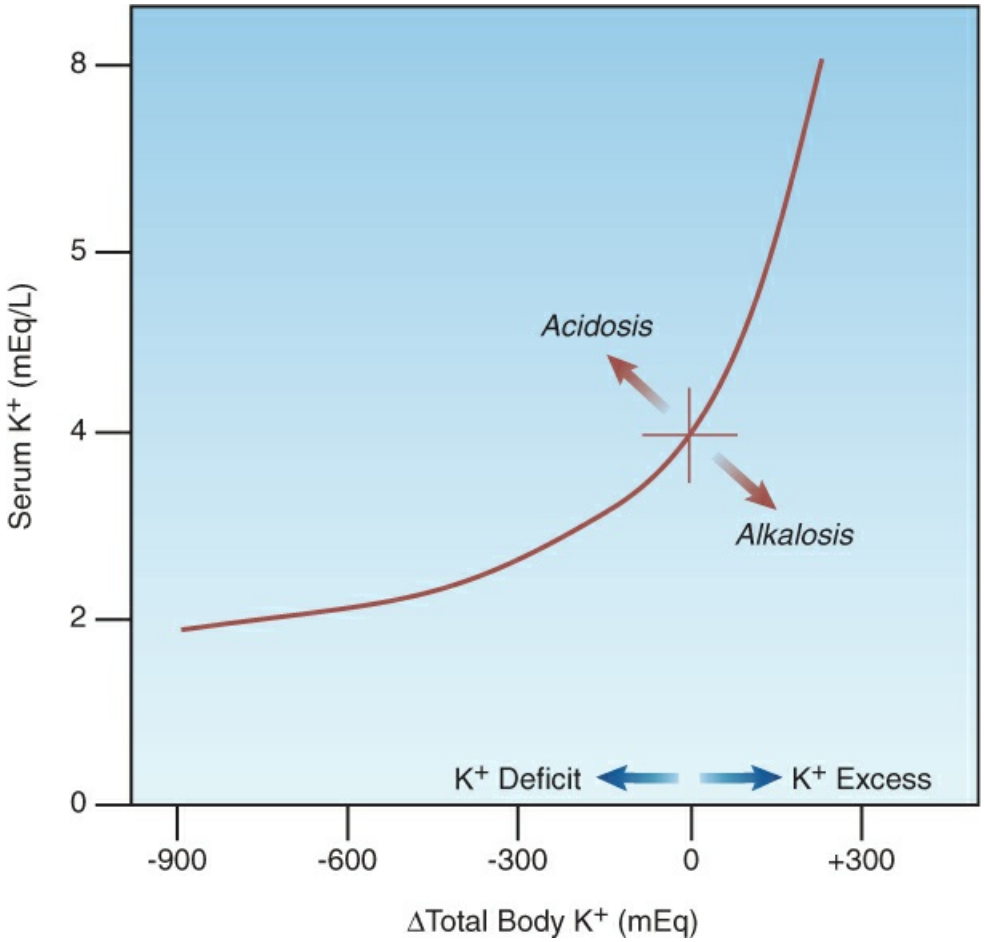

FIGURE 36.2 Relationship between the serum potassium concentration and total body potassium. Redrawn from Reference 4.

HYPOKALEMIA

Hypokalemia (serum $K^+ < 3.5$ mEq/L) can be the result of K^+ movement into cells (transcellular shift), or K^+ depletion from renal and extrarenal losses (3–6).

Transcellular Shift

The movement of K^+ into cells is facilitated by β_2-adrenergic receptors on cell membranes in muscle, and this explains the decrease in serum K^+ associated with *inhaled β_2-agonist bronchodilators* (e.g., albuterol) (7). This effect is mild (≤0.5 mEq/L) in the usual therapeutic doses (7), but is more significant when inhaled β_2-agonists are used in combination with diuretics

(8). Other factors that promote K^+ movement into cells include *alkalosis* (respiratory or metabolic), *hypothermia* (accidental or induced), and *insulin*. Alkalosis has a variable and unpredictable effect on serum K^+ (9). Hypothermia causes a transient drop in serum K^+ that resolves on rewarming (10).

Potassium Depletion

Potassium depletion can be the result of K^+ loss via the kidneys or gastrointestinal tract. The site of K^+ loss (renal or extrarenal) is usually obvious, but can be identified by measuring spot urine potassium and chloride concentrations, as shown in Figure 36.3.

Renal Potassium Loss

The leading cause of renal K^+ loss is *diuretic therapy*. Other causes likely to be seen in the ICU include nasogastric drainage, alkalosis, and magnesium depletion. Nasogastric drainage has a low concentration of K^+ (10–15 mEq/L), but the resulting loss of volume and H^+ promotes K^+ loss in the urine. The urine chloride is low (<15 mEq/L) with nasogastric drainage and alkalosis, and it is high (>25 mEq/L) with diuretic therapy and magnesium depletion. *Magnesium depletion* impairs K^+ reabsorption in the renal tubules and *may play a very important role in promoting K^+ depletion* in critically ill patients, particularly those receiving diuretics (11).

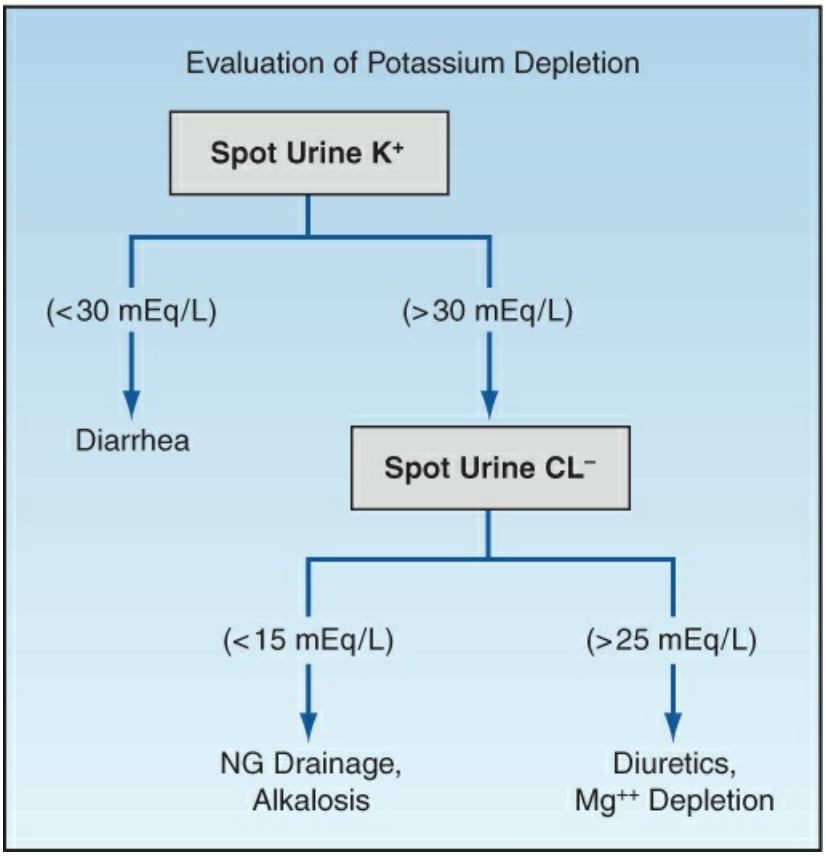

FIGURE 36.3 Evaluation to identify the site of potassium loss.

Extrarenal Potassium Loss

The major cause of extrarenal K^+ loss is *diarrhea*. Normal K^+ loss in stool is only 5–10 mEq daily. In secretory and inflammatory diarrhea, the concentration of K^+ in stool is 15–40 mEq/L, and the daily stool volume can reach 10 liters in severe cases. Therefore, K^+ losses can reach 400 mEq daily in severe cases of inflammatory or secretory diarrhea (12).

Clinical Manifestations

Severe hypokalemia (serum $K^+ < 2.5$ mEq/L) can be associated with diffuse muscle weakness (3), but in most cases, hypokalemia is asymptomatic. Abnormalities in the ECG are the major manifestation of hypokalemia, and can be present in 50% of cases (13). The ECG abnormalities include prominent U waves (more than 1 mm in height), flattening and inversion of T waves, and prolongation of the QT interval. However, these changes are not specific for hypokalemia; i.e., the T wave changes and U waves can be seen with left ventricular hypertrophy, and QT prolongation has a multitude of potential offenders.

Arrhythmias

Contrary to popular belief, *hypokalemia alone is not a risk for serious arrhythmias* (3). However, hypokalemia can add to the risk of serious arrhythmias from other conditions (e.g., myocardial ischemia) (3).

Management of Hypokalemia

The first concern in hypokalemia is to eliminate or treat any condition that promotes transcellular potassium shifts (e.g., alkalosis) (3). If the hypokalemia is due to K^+ depletion, proceed as described next.

Estimate Potassium Deficits

About 10% of total body K^+ is lost for every 1 mEq/L decrease in serum K^+ (13). For a 70 kg adult with a normal total body K^+ of 50 mEq/kg, the estimated K^+ deficits associated with progressive hypokalemia are shown in Table 36.1. Note that even mild hypokalemia (serum K^+ = 3 mEq/L) is associated with a considerable K^+ deficit (175 mEq).

TABLE 36.1 Estimated Potassium Deficits in Hypokalemia†

Serum K^+ (mEq/L)	K^+ Deficit (mEq)	Serum K^+ (mEq/L)	K^+ Deficit (mEq)
3.4	35	2.9	210
3.3	70	2.8	245
3.2	105	2.7	280
3.1	140	2.6	315
3.0	175	2.5	350

†Estimates based on a lean body weight of 70 kg and a total body K^+ of 50 mEq/kg.

Potassium Replacement

FLUIDS: The usual replacement fluid is potassium chloride, which is available as a concentrated solution (1–2 mEq/mL) in ampules containing 10, 20, 30, and 40 mEq of potassium. These solutions are *extremely hyperosmotic* (the 2 mEq/mL solution has an osmolarity of 4,000 mosm/L) and *must be diluted* (14). A potassium phosphate solution is also available that contains 4.5 mEq potassium and 3 mmol phosphate per mL, and is preferred by some for potassium replacement in diabetic ketoacidosis (because of the phosphate depletion that accompanies ketoacidosis).

RATE OF REPLACEMENT: The standard method of intravenous K^+ replacement is to add 20 mEq of K^+ to 100 mL of isotonic saline and infuse over 1 hour (15). The *maximum rate* of intravenous potassium replacement is usually set at *20 mEq/hr* (15), but dose rates of 40 mEq/hr may be necessary for severe hypokalemia, and *dose rates as high as 100 mEq/hr have been used safely* (16). Infusion through a large, central vein is preferred, if possible, because of the irritating properties of the hyperosmotic KCL solutions. However, delivery into the superior vena cava is not recommended if the desired rate of replacement exceeds 20 mEq/hr because there is a (poorly documented) risk of producing asystole.

RESPONSE: The serum K^+ may be slow to correct initially, as predicted by the flat portion of the curve in Figure 36.2. If the hypokalemia is resistant or refractory to K^+ replacement, magnesium depletion should be considered. Magnesium depletion promotes urinary K^+ loss (as described earlier), and *in patients who are magnesium deficient, hypokalemia is often resistant to K^+ replacement until the magnesium is repleted* (17). Magnesium deficiency may play an important role in diuretic-induced hypokalemia, as described in the next chapter.

HYPERKALEMIA

While hypokalemia is often well tolerated, hyperkalemia (serum $K^+ > 5.5$ mEq/L) can be a life threatening condition

Mechanisms

Hyperkalemia can be the result of potassium release from cells (transcellular shift), or impaired renal excretion of potassium. If the source of the hyperkalemia is unclear, a spot urine K^+ can be useful, as *a low urine K^+ (<30 mEq/L) is evidence of impaired renal excretion* (18). If the hyperkalemia is unexpected, the condition described next should be considered.

Factitious Hyperkalemia

Hyperkalemia can be present *ex vivo* (i.e., in the blood sample), but not *in vivo* (i.e., in the bloodstream) when K^+ is released from blood cells that are damaged when the blood specimen is obtained. This *factitious hyperkalemia* (also called "pseudohyperkalemia") usually originates from hemolysis of red blood cells, but platelets can contribute in the setting of thrombocytosis (platelet count $>500 \times 10^9$/L), and severe leukocytosis can be a factor in patients with lymphoproliferative disorders (19).

The following factors have been identified as contributing to factitious hyperkalemia (19): (*a*) the use of fist-clenching to help identify veins (which can release K^+ from skeletal muscle)

(20), (*b*) the use of excessive suction (e.g., with "vacutainers") to withdraw the blood specimen, (*c*) trauma to the specimen during transport in pneumatic tube systems (21), and (*d*) delays in processing the blood specimen.

Factitious hyperkalemia should be suspected when there is no apparent reason for hyperkalemia (the lab is often unable to identify these cases). In this situation, you should draw the blood specimen yourself, with attention to minimizing or avoiding potential contributing factors.

Transcellular Shift:

The conditions associated with K^+ movement out of cells include acidosis, rhabdomyolysis, tumor lysis syndrome, drugs, and blood transfusions.

ACIDOSIS: The presumed mechanism for the relationship between acidosis and hyperkalemia is competition between H^+ and K^+ for the same site on the membrane pump that moves K^+ into cells. However, the causal link between acidosis and hyperkalemia is being questioned because lactic acidosis is not associated with hyperkalemia (9), and respiratory acidosis has an inconsistent association with hyperkalemia (9).

TUMOR LYSIS SYNDROME: Tumor lysis syndrome is an acute, life-threatening condition that appears within 7 days after the initiation of cytotoxic therapy for selected malignancies (e.g., non-Hodgkin lymphoma). Characteristic features include the combination of hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia, often accompanied by acute kidney injury (22). Hyperkalemia is the most immediate threat to life.

DRUGS: The drugs that promote K^+ movement out of cells are listed in Table 36.2. Digitalis inhibits the membrane Na^+-K^+ exchange pump, but hyperkalemia occurs only with acute (not chronic) digitalis toxicity (23). *Succinylcholine* is an ultra short-acting neuromuscular blocking agent that inhibits the membrane Na^+–K^+ exchange pump (a depolarizing effect). This normally results in a minor increase in potassium (<1 mEq/L) that lasts 5–10 minutes (24), but life-threatening increases in serum K^+ have been reported when succinylcholine is used in patients with spinal cord injury; an effect attributed to "denervation hypersensitivity" to depolarizing agents.

TABLE 36.2 Drugs that Promote Hyperkalemia

Promote Transcellular Shift	Reduce Renal Excretion
β-Blockers	ACE inhibitors
Digitalis	ARBs
Succinylcholine	Amiloride
	NSAIDs
	Spironolactone
	TMP-SMX

ARBs = angiotensive receptor blockers, TMP-SMX = trimethoprim sulfamethoxazole.

Impaired Renal Excretion

As mentioned earlier, the capacity for urinary K^+ excretion is great enough to prevent sustained hyperkalemia after a potassium load (1). As a result, *hyperkalemia always involves (at least in part) a defect in renal potassium excretion*. This can be the result of renal disease, adrenal insufficiency, or drugs. Adrenal insufficiency impairs renal potassium excretion, but *hyperkalemia is seen only in chronic adrenal insufficiency*.

DRUGS: Drugs that impair renal potassium excretion are a common cause of hyperkalemia, and the frequent offenders are listed in Table 36.2 (24–28). All of these agents promote hyperkalemia by inhibiting some part of the renin–angiotensin–aldosterone system. (The exception is trimethoprim-sulfamethoxazole, which directly inhibits potassium secretion in the distal tubules.) Drug-induced hyperkalemia often occurs in combination with K^+ supplements or renal insufficiency.

Blood Transfusion

Hyperkalemia is a recognized (but inconsistent) complication of massive blood transfusion (i.e., blood replacement equivalent to the blood volume). The temperature used to store red blood cells (4º C) shuts off the Na^+-K^+ exchange pump in the erythrocyte cell membrane, and this results in a steady leakage of K^+ from the cells (29). The K^+ concentration in the supernatant increases steadily as the storage time increases. After 18 days of storage (the average time that blood is stored) the potassium load in one unit of packed red blood cells is 2–3 mEq (29), so massive transfusion (usually at least 6 units of red blood cells) represents a K^+ load of at least 12–18 mEq. This is a considerable load, considering that plasma contains about 9–10 mEq of K^+ in an average-sized adult.

The potassium load in transfused blood is normally cleared by the kidneys, but when systemic blood flow is compromised (which applies to most patients who need massive blood transfusions), renal K^+ excretion is impaired, and the K^+ in blood transfusions will accumulate. The transfusion volume needed to produce hyperkalemia will vary, but one study has shown that hyperkalemia begins to appear after transfusion of 7 units of red blood cells (30).

Cautopyreiophagia

In 1985, a case report was published describing a patient with severe hyperkalemia who was discovered to be ingesting 1,500 burnt match heads daily (a pica) (31). It turns out that burnt match heads are rich in potassium chlorate, and the habit of eating burnt match heads is known as *cautopyreiophagia*. This case is mentioned to demonstrate that anything is possible in clinical practice, and that there is a name for everything.

Clinical Consequences

The principal threat with hyperkalemia is slowed impulse transmission in the heart (from depolarization of cardiac muscle), which can progress to heart block and cardiac arrest.

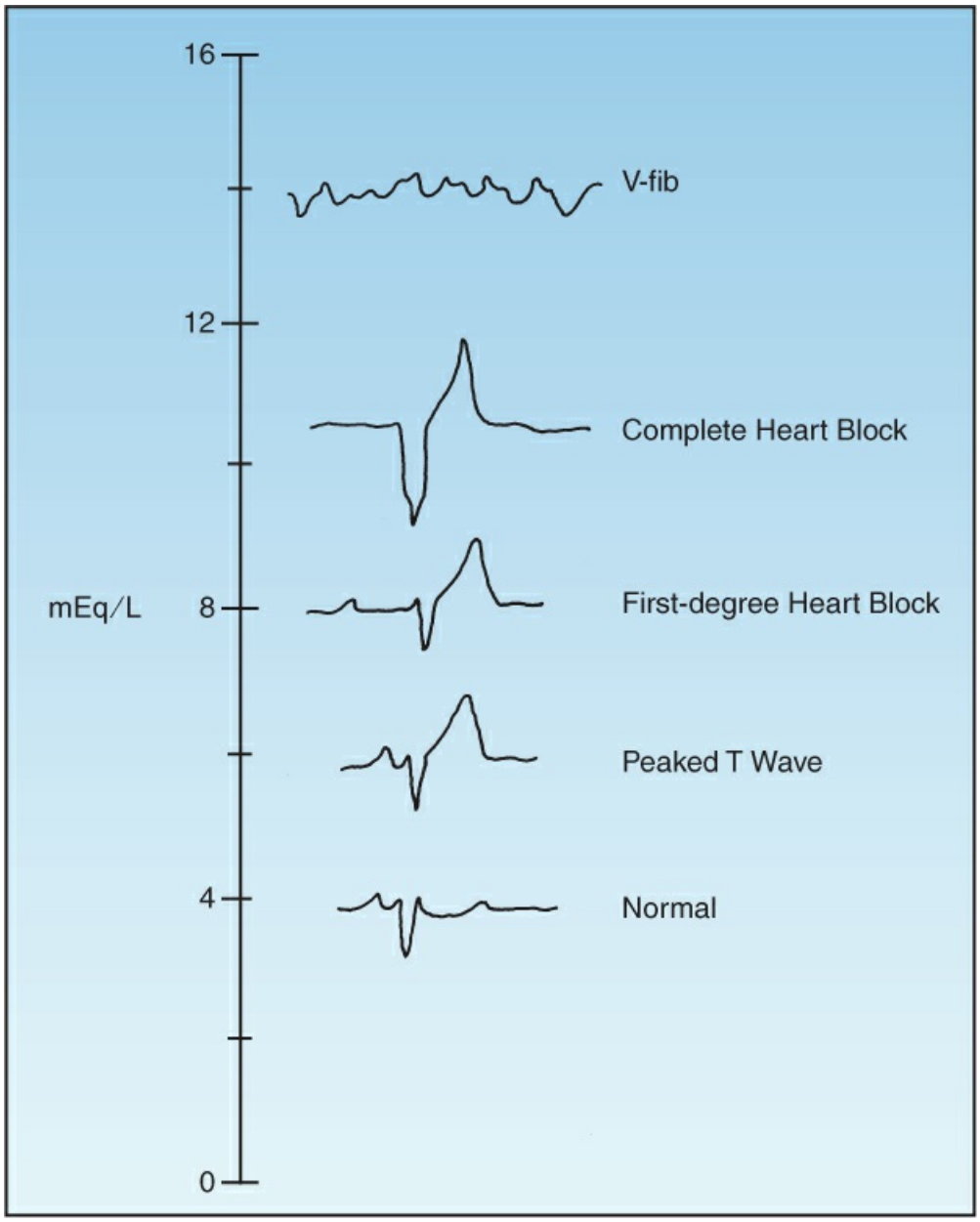

FIGURE 36.4 ECG abnormalities in progressive hyperkalemia.

ECG Changes

The expected ECG changes in progressive hyperkalemia are shown in Figure 36.4. The earliest change is the appearance of a tall, tapering (tented) T wave that is most evident in precordial leads V_2 and V_3. As the hyperkalemia progresses, the P wave amplitude decreases and the PR interval lengthens. The P waves eventually disappear and the QRS complex widens to produce a complete heart block. The final event is ventricular fibrillation or asystole.

Contrary to popular lore, *there is no predictable relationship between the severity of hyperkalemia and the presence of ECG changes* (32). For example, the traditional teaching has been that ECG changes begin to appear when the serum K^+ approaches 6 mEq/L (32), but one clinical study found that only 40% of patients with a serum K^+ above 7 mEq/L had ECG changes

(33). Another more extreme example of this is a case report of a patient with a serum K^+ of 14 mEq/L who had no ECG changes (34). This lack of correlation between the serum K and the ECG has led to the suggestion that hyperkalemia alone may not be responsible for the ECG changes.

Management of Severe Hyperkalemia

Severe hyperkalemia is defined as a serum $K^+ > 6.5$ mEq/L, or any serum K^+ that produces ECG changes (35). The management of this condition has 3 goals (36): (*a*) blocking the effects of hyperkalemia on the cardiac conduction system, (*b*) moving K^+ into cells, and (*c*) removing excess K^+ from the body. The methods used to achieve these goals are summarized in Table 36.3.

TABLE 36.3 Management of Severe Hyperkalemia

Sequential Goals	Treatment Regimen
1. Cardiac stabilization	• 10% calcium gluconate: 10 mL IV over 3 min, and repeat after 5 min, if necessary. • Use 10% calcium chloride only for circulatory collapse (has triple the Ca^{++} content of calcium gluconate).
2. Move K^+ into cells	• Regular insulin: 10 units as an IV bolus, plus 50 mL of 50% dextrose as an IV bolus. • Albuterol: 20 mg as inhaled aerosol.
3. Eliminate Excess K^+	• Sodium zirconium cyclosilicate: 10 g every 8 hr for 48 hr, then decrease dose.

Cardiac Stabilization

Hyperkalemia has a depolarizing effect on myocardial cell membranes, which closes sodium channels and slows electrical transmission (37). These effects are antagonized by the hyperpolarizing effects of calcium, which is the treatment of choice for the cardiotoxic effects of hyperkalemia.

REGIMEN: Calcium is available in two intravenous preparations: *10% calcium gluconate*, which contains 9 mg/mL of elemental calcium in a 10 mL ampule, and *10% calcium chloride*, which contains 27 mg/mL of elemental calcium in a 10 mL ampule. Therefore, the calcium chloride preparation delivers three times more calcium than the calcium gluconate preparation. The less concentrated gluconate preparation is used in most instances, while the calcium chloride is reserved for cases of cardiovascular collapse or cardiac arrest.

The calcium regimen is shown in Table 36.3. The calcium effect should be evident after a few minutes. However, the effect dissipates in 30–60 minutes, so the other interventions in Table 36.3 should be combined with the calcium treatment.

INDICATIONS: The published indications for calcium include a serum $K^+ > 6.5$ mEq/L (with or without ECG changes), and ECG changes (regardless of the serum K^+) (35). However, some prefer to use calcium only when there are appropriate ECG changes; a strategy that seems appropriate, given the poor correlation between the serum K^+ level and the risk of ECG changes.

DIGITALIS: Calcium has traditionally been contraindicated for managing the hyperkalemia associated with digitalis toxicity (because digitalis toxicity poisons the membrane pump, which leads to life-threatening calcium accumulation in cells). However, retrospective studies have revealed numerous instances where intravenous calcium was given to patients with digitalis toxicity, without harm (38).

Moving Potassium Into Cells

There are three methods that are used to move K^+ into cells.

INSULIN-DEXTROSE: Insulin drives K^+ into skeletal muscle cells by activating the membrane Na^+–K^+ exchange pump, and the insulin-dextrose regimen in Table 36.3 will decrease the serum K^+ by at least 0.6 mEq/L (35). However, this effect is temporary (peak effect at 30–60 min), so measures that promote K^+ elimination should be started as well.

β_2-AGONISTS: Inhaled β_2-agonists (e.g., albuterol) produce a small decrease in plasma K^+ (<0.5 mEq/L) in therapeutic doses (7). The dose needed to produce a significant (0.5–1 mEq/L) drop in serum K^+ is at least 4 times the therapeutic dose (35), and this can produce unwanted side effects (e.g., tachycardia). Despite this risk, inhaled β_2-agonists have become part of the standard management protocol for severe hyperkalemia in many emergency departments. However, these agents should never be used alone to manage severe hyperkalemia.

SODIUM BICARBONATE: Sodium bicarbonate has been used to move K^+ into cells by promoting alkalosis, but there are two reasons why bicarbonate is not advised in this setting: (*a*) short-term infusions of sodium bicarbonate (up to four hours) have no effect on serum K^+ levels in the absence of a metabolic acidosis (35) and (*b*) bicarbonate can form complexes with calcium, which is counterproductive when calcium is used to antagonize the effects of hyperkalemia.

Eliminating Excess Potassium

Excess K^+ can be removed via the bowel using cation (Na-K) exchange resins, or it can be removed directly from the bloodstream with hemodialysis.

CATION EXCHANGE RESINS: Sodium polystyrene sulfonate or SPS (Kayexalate®) is the original cation exchange resin approved for use in severe hyperkalemia. It can be given orally (as a slurry) in a dose of 15 g every 6 hours, or rectally (as a retention enema) in a dose of 30–50 g every 6 hours. Although once the standard of care for severe hyperkalemia, the use of this agent is questioned because of uncertain efficacy, slow onset of action, and reports of necrotic lesions in the bowel linked to its use (39).

Another cation exchange resin, *sodium zirconium cyclosilicate* or SZC (Lokelma®) has been effective in managing hyperkalemia in outpatients (40) and recently has been shown to be equivalent to SPS for acute management of hyperkalemia (41). The SCZ resin does not have the adverse risks associated with SPS, and seems to be the favored choice at the present time. The dose is 10 grams orally, given 3 times daily for 48 hours (then the dose is reduced as needed). A clinically significant effect is reported after one hour (40).

HEMODIALYSIS: The most effective method of potassium removal is hemodialysis, which can

produce a 1 mEq/L drop in serum K^+ after one hour, and a 2 mEq/L drop after 3 hours (35).

A FINAL WORD

Tip of the Iceberg

Considering that only 2% of the potassium in the body is outside cells, and that only 20% of the extracellular potassium is in plasma, monitoring the plasma K^+ gives us information about <1% of the potassium in the body. That might explain why hypokalemia is often clinically silent, and why there is a poor correlation between the severity of hyperkalemia and the presence of ECG changes.

That said, there are a few points in this chapter that deserve emphasis:

. Hypokalemia is not a risk for serious arrhythmias unless combined with a drug or clinical condition that can trigger arrhythmias (3).

. When hypokalemia is refractory to K^+ replacement, Mg^{++} deficiency is likely the source of the problem (17).

. When using calcium to antagonize the cardiac effects of hyperkalemia, make sure you know which preparation you are using (calcium gluconate or calcium chloride), since calcium chloride has three times more elemental calcium than calcium gluconate.

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Chapter 37

Magnesium

You can know the name of a bird in all the languages of the world, but you'll know absolutely nothing about the bird. So let's look at the bird and see what it's doing – that's what counts.

Richard Feynman (*a*)

Magnesium is essential for energy utilization in the organic world. To begin with, magnesium is the heart of the chlorophyll molecule in green plants, which captures the radiant energy in sunlight and stores it in the carbon bonds that hold carbohydrates together. Aerobic organisms then transfer this energy to adenosine triphosphate (ATP), and the release of energy from ATP requires magnesium (which is an essential cofactor for ATPase enzymes). Thus, magnesium is essential for providing us with energy from the sun, and for allowing us to utilize this energy to sustain life.

Magnesium is also essential for the proper functioning of the Na^+–K^+ exchange pump (which is a magnesium-dependent ATPase) that is responsible for the electrical gradient across cell membranes. As a result, magnesium plays an important role in the activity of excitable tissues (1–4). Magnesium also regulates the movement of calcium into smooth muscle cells, which gives it a pivotal role in the maintenance of cardiac contractile strength and peripheral vascular tone (4).

Now that's an element.

MAGNESIUM BASICS

The distribution of magnesium (Mg) in the human body is shown in Table 37.1 (5). The average-sized adult contains approximately 24 g (1 mole, or 2,000 mEq) of magnesium; a little over half is located in bone, whereas *less than 1% is located in plasma*. This lack of representation in the plasma limits the value of the plasma Mg as a measure of total body Mg (similar to the limitation described for the plasma K^+ measurement). One consequence of this is that *plasma Mg levels can be normal in the face of total body Mg depletion* (5,6).

Serum Magnesium

Serum is favored over plasma for measuring Mg levels because the anticoagulant used for plasma samples can be contaminated with citrate or other anions that bind Mg (5). The reference range for serum Mg depends on the daily Mg intake, which varies according to geographic region. The normal range of serum Mg for healthy adults in the United States is shown in Table 37.2 (7).

Converting Units

The clinical laboratory typically reports the serum Mg concentration in mg/dL (because Mg is partially bound to plasma proteins), while the medical literature typically uses mEq/L for the serum Mg concentration. The conversion is as follows:

$$\text{mEq/L} = \frac{\text{mg/dL} \times 10}{\text{mol wt}} \times \text{valence} \tag{37.1}$$

where mol wt is the molecular weight (atomic weight in the case of Mg) and valence is the number of charges on the atom or molecule. Magnesium has an atomic weight of 24 and a valence of 2, so a serum Mg concentration of 1.7 mg/dL is equivalent to (1.7 × 10)/24 × 2 = 1.4 mEq/L.

To complicate matters further, the International System of Units (SI units) uses mmol/L to express the serum Mg concentration. The conversion is: mmol/L = mEq/L × 0.5.

TABLE 37.1 Magnesium Distribution in a 70 kg Adult

Component	Mg Content (mEq)	% Total Body Mg
Bone	1,060	53
Muscle	540	27
Soft Tissue	384	19
Erythrocytes	10	0.7
Plasma	6	0.3
Total	2,000	100%

From Reference 5.

Ionized Magnesium

About 67% of the Mg in plasma is in the ionized (active) form (see Table 37.2), and the remaining 33% is either bound to plasma proteins, or chelated with divalent anions such as phosphate and sulfate (8). The standard assay for Mg measures all three fractions, so in cases of hypomagnesemia, it is not possible to determine if the problem is a decrease in the ionized (active) fraction, or a decrease in the bound fractions (e.g., hypoproteinemia) (9). The level of ionized Mg can be measured with an ion-specific electrode, but this is not routinely available.

However, the clinical significance of monitoring ionized Mg versus total Mg is unclear.

TABLE 37.2 Reference Ranges for Serum Magnesium

	mg/dL	mEq/L	mmol/L
Total Serum Mg	1.7–2.4	1.4–2.0	0.7–1.0
Ionized Mg	—	0.8–1.1	0.4–0.6

Urinary Magnesium

Only small quantities of Mg are normally excreted in the urine (i.e., about 5–15 mEq in 24 hrs) (7). When Mg intake is deficient, the kidneys conserve Mg further, and urinary Mg excretion falls to negligible levels. This is shown in Figure 37.1 (10). Note that the plasma Mg remains in the normal range one week after starting a magnesium-free diet, while the urinary Mg excretion has dropped to negligible levels. This illustrates the relative value of urinary Mg excretion in the early detection of Mg deficiency.

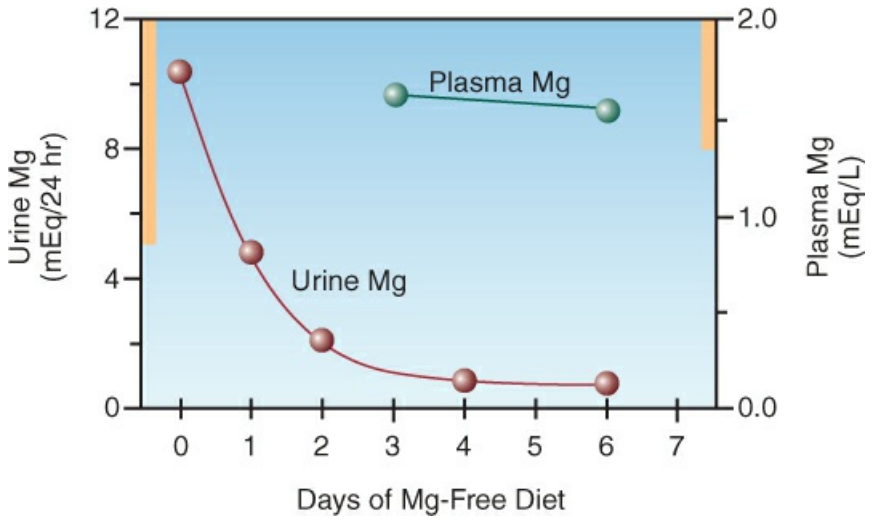

FIGURE 37.1 Urinary magnesium excretion and plasma magnesium levels in a healthy volunteer placed on a magnesium-free diet. Solid bars on the vertical axis represent the normal range for each variable. Adapted from Reference 10.

MAGNESIUM DEFICIENCY

Hypomagnesemia (total serum Mg < 1.7 mg/dL or <0.7 mmol/L) is reported in as many as 65% of ICU patients (2,11), and the frequency of magnesium deficiency is likely to be higher (because magnesium deficiency can exist without hypomagnesemia).

Predisposing Conditions

The most common predisposing conditions for magnesium depletion in the ICU are listed in Table 37.3.

TABLE 37.3 Markers of Possible Magnesium Depletion§	
Predisposing Conditions	**Clinical Findings**
Drug Therapy: Furosemide (50%) Aminoglycosides (30%) Proton Pump Inhibitors Insulin Alcohol Use Disorder (44%) Diabetes Mellitus Diarrhea (secretory) Acute MI (80%)	*Electrolyte Disorders*: Hypokalemia (40%) Hypophosphatemia (30%) Hyponatremia (27%) Hypocalcemia (22%) *Cardiac Manifestations:* Coronary Ischemia Arrhythmias Digitalis Toxicity Hyperactive CNS Syndrome

§Parentheses indicate frequency of associated hypomagnesemia.

Diuretic Therapy

Diuretics are a leading cause of Mg deficiency in ICUs. Diuretic-induced inhibition of sodium reabsorption also interferes with magnesium reabsorption, and the resultant urinary magnesium losses can parallel urinary sodium losses. Urinary magnesium excretion is most pronounced with the loop diuretics (furosemide and ethacrynic acid). *Magnesium deficiency has been reported in 50% of patients receiving chronic therapy with furosemide* (12). Thiazides have a similar tendency to produce hypomagnesemia (3). Magnesium depletion does not occur with potassium-sparing diuretics (13).

Other Drugs

The following drugs are notable for causing hypomagnesemia:

. The aminoglycosides block magnesium reabsorption in the ascending loop of Henley, and hypomagnesemia has been reported in 30% of patients receiving aminoglycosides (14).

. Proton pump inhibitors and metformin can produce hypomagnesemia by blocking magnesium absorption in the GI tract (3,15).

. Insulin and epinephrine produce hypomagnesemia by shifting magnesium into cells (3).

. Cisplatin and carboplatin can cause hypomagnesemia by promoting renal magnesium excretion (3).

Alcohol-Use Disorder

Hypomagnesemia is reported in 44% of patients with chronic alcohol-use disorder (16). Multiple factors are involved, including malnutrition, chronic diarrhea, and a blunted renal response to magnesium depletion.

Secretory Diarrhea

Secretions from the lower GI tract are rich in magnesium (10–14 mEq/L) (17), and secretory diarrhea can be accompanied by profound magnesium depletion (18). Upper GI tract secretions are not rich in magnesium (1–2 mEq/L), so vomiting does not pose a risk for magnesium depletion.

Diabetes Mellitus

Magnesium depletion is common in insulin-dependent diabetic patients, probably as a result of urinary Mg losses that accompany glycosuria (19). Hypomagnesemia is reported in only 7% of admissions for diabetic ketoacidosis, but the incidence increases to 50% over the first 12 hours after admission (20), probably as a result of insulin-induced movement of magnesium into cells.

Acute Myocardial Infarction

Hypomagnesemia is reported in as many as 80% of patients with acute myocardial infarction (21). Several mechanisms may be involved, including an intracellular shift of Mg from excess catecholamines.

Clinical Manifestations

There are no specific clinical manifestations of Mg deficiency, but the following clinical findings can increase suspicion of Mg deficiency.

Other Electrolyte Abnormalities

Magnesium depletion is often accompanied by a decrease in serum levels of sodium, potassium, phosphate, and calcium (see Table 37.3) (22).

HYPOKALEMIA: Hypokalemia is reported in 40% of cases of Mg depletion (22). More importantly, *the hypokalemia that accompanies Mg depletion can be refractory to K^+ replacement*, and Mg replacement is necessary before the hypokalemia can be corrected (23).

HYPOCALCEMIA: Magnesium depletion can cause hypocalcemia as a result of impaired parathormone release (24) combined with an impaired end-organ response to parathormone (25). As with the hypokalemia, *the hypocalcemia that accompanies Mg depletion is difficult to correct until Mg deficits are corrected*.

HYPOPHOSPHATEMIA: Phosphate depletion is a cause rather than an effect of Mg depletion. The mechanism is enhanced renal Mg excretion (26).

Arrhythmias

Magnesium depletion will depolarize cardiac cells and promote arrhythmias. The following information regarding Mg and arrhythmias deserves mention:

. Both digitalis and Mg deficiency act to inhibit the membrane pump, so Mg deficiency will promote digitalis cardiotoxicity. Intravenous magnesium can suppress digitalis-toxic arrhythmias, even when serum Mg levels are normal (27).

. Intravenous magnesium can also abolish refractory ventricular arrhythmias when serum Mg levels are normal (28). This effect may be due to a membrane-stabilizing effect of magnesium that is unrelated to Mg repletion.

. The most cited arrhythmia linked to magnesium depletion is polymorphic ventricular tachycardia, better known as *torsade de pointes*. The role of magnesium in this arrhythmia is

presented in Chapter 19 (see Figure 19.9).

Neurologic Manifestations

The neurologic manifestations of magnesium deficiency can include altered mentation, tremors, hyperreflexia, and generalized seizures. All are uncommon and nonspecific, but the following neurotoxic syndromes deserve mention.

HYPERACTIVE CNS SYNDROME: A magnesium-related neurologic syndrome has been reported that presents with ataxia, slurred speech, excessive salivation, diffuse muscle spasms, generalized seizures, and progressive obtundation (29). The symptoms are often triggered by loud noises or bodily contact. This syndrome is associated with reduced Mg levels in cerebrospinal fluid, and it resolves with Mg infusions. The prevalence of this disorder is unknown.

WERNICKE'S: Magnesium is required for the transformation of thiamine into thiamine pyrophosphate, so *magnesium deficiency can promote thiamine deficiency, even in the face of adequate thiamine intake* (30,31).

Magnesium Replacement

The daily requirement for magnesium in healthy adults is 420 mg (35 mEq) for males and 320 mg (26 mEq) for females (see Table 37.4) (32). (*Note:* The daily requirements for magnesium are likely to be higher in ICU patients because conditions that predispose to magnesium depletion are common in these patients.) The popular oral preparation for magnesium maintenance therapy is magnesium oxide, available in 400 mg tablets, which contain 241 mg (20 mEq) of elemental magnesium (33).

Absorption of magnesium from the GI tract can be erratic in ICU patients, so intravenous magnesium is used for magnesium replacement. The standard intravenous preparation is magnesium sulfate ($MgSO_4$), which is available as magnesium sulfate heptahydrate ($MgSO_4 \cdot 7H_2O$) (34). *Each gram of this $MgSO_4$ preparation has about 8 mEq (4 mmol) of elemental magnesium* (whereas one gram of $MgSO_4$ has about twice the amount of elemental magnesium) (34). Ringer's solutions should not be used as the diluent for $MgSO_4$ because the calcium in Ringer's solutions will counteract the actions of magnesium.

TABLE 37.4 Magnesium Preparations and Daily Requirements

	Elemental Mg
Normal Daily Requirements:	
Adult Males (>30 yrs)	420 mg (35 mEq, 17.5 mmol)
Adult Females (>30 yrs)	320 mg (26 mEq, 13 mmol)
Oral Preparation:	
Magnesium Oxide (400 mg)	241 mg (20 mEq, 10 mmol)
IV Preparation:	
Magnesium Sulfate ($MgSO_4$)	98 mg (8 mEq, 4 mmol)/gram)§

The magnesium content is for magnesium sulfate heptahydrate ($MgSO_4 \cdot 7\ H_2O$), which is the usual $MgSO_4$

preparation.

The following magnesium replacement protocols are recommended for patients with normal renal function (35). (*Note:* The $MgSO_4$ in these recommendations is for the $MgSO_4 \cdot 7H_2O$ preparation.)

Mild Hypomagnesemia

The following dosing regimen can be used for a serum Mg of 1–1.4 mEq/L (1.2– 1.7 mg/dL, or 0.5–1 mmol/L) that is clinically silent:

. Assume a total magnesium deficit of 1–2 mEq/kg.

. Because 50% of the infused magnesium can be lost in the urine, assume that the total magnesium requirement is twice the magnesium deficit.

. Replace 1 mEq/kg for the first 24 hours, and 0.5 mEq/kg daily for the next 3–5 days.

Moderate Hypomagnesemia

The following protocol is recommended for a serum Mg < 1 mEq/L (<1.2 mg/dL, or <0.5 mmol/L), or for hypomagnesemia that is accompanied by other electrolyte abnormalities:

. Add 6 g $MgSO_4$ (48 mEq of Mg) to 250 or 500 mL isotonic saline and infuse over 3 hours.

. Follow with 5 g $MgSO_4$ (40 mEq of Mg) in 250 or 500 mL isotonic saline infused over the next 6 hours.

. Continue with 5 g $MgSO_4$ every 12 hours (by continuous infusion) for the next 5 days.

Life-Threatening Hypomagnesemia

The following is recommended for hypomagnesemia associated with serious cardiac arrhythmias (e.g., torsade de pointes) or generalized seizures:

. Infuse 2 g $MgSO_4$ (16 mEq, or 8 mmol of Mg) intravenously over 2–5 minutes.

. Follow with 5 g $MgSO_4$ (40 mEq, or 20 mmol of Mg) in 250 or 500 mL isotonic saline and infuse over the next 6 hours.

. Continue with 5 g $MgSO_4$ every 12 hours (by continuous infusion) for the next 5 days.

Hypomagnesemia and Renal Insufficiency

Hypomagnesemia is not common in patients with renal insufficiency but it can occur when extrarenal Mg losses are combined with a creatinine clearance of 30–50 mL/min. When magnesium is replaced in patients with renal insufficiency, no more than 50% of the magnesium in the standard replacement protocols should be administered (35), and the serum Mg should be monitored carefully.

Monitoring Magnesium Replacement

Serum Mg levels will rise after the initial magnesium bolus, but will begin to fall after 15

minutes. Therefore, it is important to follow the bolus dose with a continuous magnesium infusion. Serum Mg levels may normalize after 1 to 2 days, but it will take several days to replenish the total body Mg stores. The magnesium retention test in Table 37.5 can be valuable for identifying the end-point of Mg replacement therapy (3,36).

TABLE 37.5 Magnesium Retention Test

Protocol:

1. Add 6 grams $MgSO_4$ (24 mmol or 48 mEq elemental Mg) to 250 mL of isotonic saline and infuse over 1 hr.
2. Collect urine for 24 hrs, beginning with the onset of the magnesium infusion.

Results:

1. Urinary Mg excretion ≤12 mmol (24 mEq) in 24 hrs (i.e., ≤50% of the infused Mg) is evidence of continued Mg depletion.
2. Urinary Mg excretion >19 mmol (38 mEq) in 24 hrs (i.e., >80% of the infused Mg) indicates sufficient Mg stores.

From Reference 36.

Magnesium Retention Test

The magnesium retention test evaluates the percentage of an infused magnesium load that is excreted in the urine. The normal rate of magnesium reabsorption is close to the maximum rate (Tmax), so most of an infused magnesium load will be excreted in the urine when magnesium stores are normal. However, when magnesium stores are deficient, the magnesium reabsorption rate is much lower than the Tmax, so more of the infused magnesium will be reabsorbed, and less will be excreted in the urine. *Magnesium deficiency is likely when less than 50% of the infused Mg is recovered in the urine, and is unlikely when more than 80% of the infused Mg is excreted in the urine* (36,37).

The magnesium retention test has one unfortunate shortcoming: i.e., it can be unreliable when renal function is impaired (which is the case in many ICU patients).

HYPERMAGNESEMIA

Hypermagnesemia is uncommon in hospitalized patients, with one survey showing a prevalence of 5% (38).

Predisposing Conditions

Most cases of hypermagnesemia are the result of impaired renal function (i.e., creatinine clearance <30 mL/min) combined with a source of magnesium intake (e.g., from magnesium-containing antacids or laxatives) (3).

Massive Hemolysis

The Mg concentration in erythrocytes is approximately three times greater than in serum (39), so hemolysis can increase the serum Mg. The serum Mg is expected to rise by 0.1 mEq/L for every 250 mL of erythrocytes that lyse completely (39), so hypermagnesemia is expected only with

massive hemolysis.

Other Conditions

Other conditions associated with (mild) hypermagnesemia are adrenal insufficiency, hyperparathyroidism, and lithium intoxication (3).

Clinical Features

The clinical consequences of progressive hypermagnesemia are listed below (39).

Threshold Serum Mg	*Manifestation*
>4 mEq/L	Hyporeflexia
>5 mEq/L	1st° AV Block
>10 mEq/L	Complete Heart Block
>13 mEq/L	Cardiac Arrest

Magnesium has been described as *nature's physiologic calcium blocker* (40), and most of the serious consequences of hypermagnesemia are the result of calcium antagonism in the AV conduction system of the heart. Depressed contractility and vasodilation are not prominent.

Management

Hemodialysis is the treatment of choice for severe hypermagnesemia. Intravenous calcium gluconate (1 g IV over 2 to 3 minutes) can be used to antagonize the cardiovascular effects of hypermagnesemia *temporarily*, until dialysis is started (41). If fluids are permissible and some renal function is preserved, aggressive volume infusion combined with furosemide may be effective in reducing the serum magnesium levels in less advanced cases of hypermagnesemia.

A FINAL WORD

Magnesium often takes a back seat to other cations like sodium and potassium, but considering the vital roles of magnesium described in the introduction to this chapter, it deserves much more attention that it receives. The following are some specific points about magnesium that warrant emphasis:

. The serum magnesium level can be normal in patients who are magnesium depleted.

. Hypomagnesemia is reported in over 50% of ICU patients, and the frequency of magnesium depletion is likely to be even higher (because of statement #1). Diuretic therapy with furosemide is the leading cause of magnesium depletion in ICUs.

. Magnesium depletion should be suspected in any patient with diuretic-induced hypokalemia, especially when hypokalemia is refractory to potassium replacement.

. Magnesium replacement will correct the serum magnesium before total body stores of magnesium are replenished. The best indicator of magnesium repletion is the urinary retention

test (see Table 37.5).

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Chapter 38

Calcium and Phosphorus

Nature never deceives us, it is always we who deceive ourselves.

Jean Jacques Rousseau (1754)

Calcium and phosphorus are responsible for much of the structural integrity of the bony skeleton. Although neither element is found in abundance in soft tissue, both have important roles in vital cell functions. Phosphorus participates in aerobic energy production, whereas calcium participates in blood coagulation, neuromuscular transmission, and smooth muscle contraction. In light of these roles, it is surprising that abnormalities in calcium and phosphorus balance are devoid of adverse consequences in most patients.

CALCIUM BASICS

Calcium is the most abundant electrolyte in the human body, (the average adult has more than half a kilogram of calcium), but 99% is in bone (1,2). Parathyroid hormone and vitamin D (calcitriol) promote calcium resorption from bone and thereby maintain plasma calcium levels, while calcitonin (from the thyroid gland) has the opposite effect and inhibits calcium release from bone.

Plasma Calcium

The calcium in plasma is present in three forms, as depicted in Figure 38.1. Approximately half of the calcium is ionized (biologically active) and the remainder is either bound to albumin (80%) or complexed with sulfate and phosphate anions (20%) (1,2). The concentration of total and ionized calcium in plasma is shown in Table 38.1. These values may vary slightly in different clinical laboratories.

TABLE 38.1 Normal Ranges for Calcium and Phosphate in Blood

Serum Electrolyte	Traditional Units (mg/dL)	Conversion Factor*	SI Units (mmol/L)
Total Calcium	9.0–10.0	0.25	2.25–2.50

Ionized Calcium	4.6–5.0	0.25	1.15–1.25
Phosphorus	2.5–5.0	0.32	0.8–1.6

*Multiply traditional units by conversion factor to derive SI Units or divide SI Units by conversion factor to derive traditional units.

Total vs. Ionized Calcium

The calcium assay used by most clinical laboratories measures all three fractions of calcium in plasma, and this can be misleading in patients with hypoalbuminemia. This is demonstrated in Figure 38.1, which shows that a decrease in plasma albumin will decrease the total calcium concentration without affecting the ionized calcium concentration. Since the ionized calcium is the physiologically active fraction, the hypocalcemia caused by hypoalbuminemia is not physiologically significant.

A variety of correction factors have been proposed for adjusting the plasma calcium concentration in patients with hypoalbuminemia. However, none of these are reliable (3,4), and *the measurement of ionized calcium with ion-specific electrodes is necessary for accuracy.*

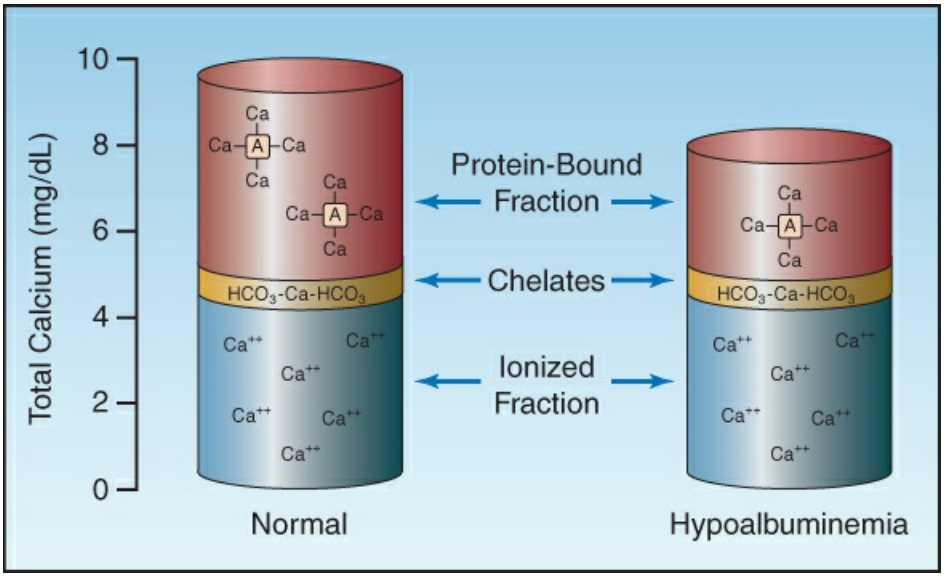

FIGURE 38.1 The three fractions of calcium in plasma and the contribution of each to the total calcium concentration. The column on the right shows how a decrease in plasma albumin can reduce the total plasma calcium without influencing the ionized (active) fraction.

Some precautions are necessary when collecting blood samples for an ionized calcium measurement. Loss of carbon dioxide from a blood sample could falsely lower the ionized calcium (by increasing calcium binding to albumin), so it is important to avoid gas bubbles in the blood sample. Anticoagulants (e.g., heparin, citrate, and EDTA) can bind calcium, so blood samples should not be placed in collection tubes that contain these anticoagulants. Tubes with red stoppers ("red top" tubes) contain silicone and are adequate for measuring ionized calcium in serum samples.

IONIZED HYPOCALCEMIA

Ionized hypocalcemia (plasma ionized Ca^{++} < 4.6 mg/dL or <1.7 mmol/L) is extremely common in ICUs (5–7), with one multicenter survey reporting an incidence of 88% in ICU patients (7). The conditions that predispose to ionized hypocalcemia in ICU patients are listed in Table 38.2.

Predisposing Conditions

Hypoparathyroidism is a leading cause of hypocalcemia in outpatients, but is not a consideration in the ICU unless a patient has had recent thyroid surgery.

TABLE 38.2 Causes of Ionized Hypocalcemia in the ICU

Most Common	Others
Alkalosis	Massive Transfusion
Magnesium Deficiency	Pancreatitis
Renal Failure	Rhabdomyolysis
Sepsis	Tumor Lysis Syndrome

Alkalosis

Alkalosis promotes the binding of calcium to albumin, and thereby reduces the fraction of ionized calcium in blood. Infusions of sodium bicarbonate can also promote ionized hypocalcemia because the infused bicarbonate forms complexes with free calcium.

Magnesium Depletion

Magnesium depletion promotes hypocalcemia by inhibiting parathormone secretion (8) and reducing end organ responsiveness to parathormone (9). *Hypocalcemia from magnesium depletion is refractory to calcium replacement therapy, and magnesium replacement often corrects the hypocalcemia*.

Systemic Inflammation

Systemic inflammation promotes ionized hypocalcemia via the actions of cytokines to stimulate calcitonin release and blunt the response to parathormone (5,6). This makes sepsis a common cause of hypocalcemia in the ICU.

Renal Failure

Renal failure can promote ionized hypocalcemia as a result of phosphate retention and impaired conversion of vitamin D to its active form in the kidneys. However, the acidosis in renal failure will decrease the binding of calcium to albumin, which helps to maintain ionized calcium levels.

Massive Transfusion

Ionized hypocalcemia is almost universal in trauma victims who receive massive blood transfusions, and the hypocalcemia can be severe (<0.9 mmol/L) in over half of the patients (10). The culprit is the citrate anticoagulant used in banked blood, which complexes with calcium.

Others

Other sources of ionized hypocalcemia include acute pancreatitis (usually severe),

rhabdomyolysis, and tumor lysis syndrome.

Clinical Manifestations

Potential consequences of hypocalcemia include enhanced cardiac and neuromuscular excitability, and reduced contractile force in cardiac muscle and vascular smooth muscle. However, *most cases of ionized hypocalcemia in the ICU have no apparent adverse consequences* (5–7), and this has prompted the suggestion that routine monitoring of calcium should be abandoned in ICU patients (6).

Neuromuscular

The neuromuscular manifestations of hypocalcemia that are often cited include hyperreflexia, paresthesias, seizures and tetany (11). However, these rarely occur in ICU patients (5–7). *Chvostek's sign* (facial twitching when tapping the facial nerve) is cited as a sign of hypocalcemia, but this sign *has been reported in over 50% of healthy subjects with normocalcemia* (12). Trousseau's sign (i.e., carpopedal spasms in the same arm where a blood pressure cuff is inflated to exceed the systolic pressure) is also considered a reliable sign of hypocalcemia (13), but this is poorly documented.

Cardiovascular

The cardiovascular complications of hypocalcemia include hypotension, decreased cardiac output, and ventricular ectopic activity. However, these complications are rare, and are reported only in cases of extreme ionized hypocalcemia (<0.65 mmol/L) (14).

Calcium Replacement Therapy

Calcium replacement therapy is recommended only in the rare instances where hypocalcemia causes a serious adverse reaction. (The principal use of intravenous calcium is to block the cardiotoxic effects of hyperkalemia.) If calcium replacement is necessary, the intravenous calcium solutions and a recommended dosing regimen are shown in Table 38.3.

TABLE 38.3 Intravenous Calcium Replacement Therapy

Solution	Elemental Ca	Unit Volume	Osmolarity
10% Calcium chloride	27 mg/mL	10 mL ampules	2,000 mosm/L
10% Calcium gluconate	9 mg/mL	10 mL ampules	680 mosm/L

For symptomatic hypocalcemia:

1. Give a bolus dose of 200 mg elemental calcium (e.g., 22 mL of 10% calcium gluconate) in 100 mL isotonic saline over 10 minutes.
2. Follow with a continuous infusion of 1–2 mg/kg per hour for 6–12 hrs.
3. Monitor ionized calcium levels hourly for the first few hours.

Calcium Salt Solutions

The calcium solutions for intravenous use are 10% calcium chloride and 10% calcium gluconate. *Calcium chloride contains three times more elemental calcium than calcium gluconate*, but calcium gluconate is usually preferred because it has a lower osmolarity, and is less irritating

when injected.

Dosing Regimen

A bolus dose of 200 mg elemental calcium (diluted in 100 mL isotonic saline and given over 5–10 minutes) should raise the total serum calcium by 0.5 mg/dL (14), but levels will begin to fall after 30 minutes. Therefore, the bolus dose of calcium should be followed by a continuous infusion at a dose rate of 1–2 mg/kg/hr (elemental calcium) for at least 6 hours. Individual responses will vary, so calcium dosing should be guided by the level of ionized calcium in blood.

CAUTION: Intravenous calcium has been shown to promote multiorgan failure in critically ill patients (15), possibly by promoting intracellular calcium overload, which can produce a lethal cell injury (16).

Summation

Hypocalcemia in ICU patients is considered to be more of a general marker of illness than a pathological condition that requires treatment. Most cases of symptomatic hypocalcemia occur in patients with hypoparathyroidism, which is rarely encountered in the ICU.

HYPERCALCEMIA

Hypercalcemia is usually the result of a hyperparathyroidism or malignancy, with malignancy being the usual culprit in ICU patients (17). The malignancies associated with hypercalcemia include multiple myeloma, breast, lung, and ovarian cancer, squamous cell carcinoma of the head and neck, and some lymphomas (18).

Clinical Manifestations

The manifestations of hypercalcemia are varied and nonspecific. Potential manifestations can be organized as follows:

. *Gastrointestinal:* nausea, vomiting, constipation, and ileus.

. *Cardiovascular:* hypovolemia, hypotension, and shortened QT interval.

. *Renal:* polyuria and acute kidney injury.

. *Neurologic:* confusion, depressed consciousness, and coma.

Manifestations usually begin to appear when the serum calcium is >12.5 mg/dL (or the ionized calcium is >3.0 mmol/L), and they are almost always present when the serum calcium is >14 mg/dL (or the ionized calcium is >3.5 mmol/L) (17). Manifestations are more likely to appear with rapid increases in serum calcium.

Management

Treatment is indicated when the serum calcium is >14 mg/dL (or ionized calcium is >3.5 mmol/L), or when there are neurologic symptoms. The treatment options for hypercalcemia are summarized in Table 38.4

Saline Infusion

Hypercalcemia promotes calcium loss in the urine (hypercalciuria), and this produces an osmotic diuresis that can result in hypovolemia. When this occurs, urinary calcium excretion decreases, resulting in a more rapid rise in the serum calcium. Therefore, *volume resuscitation to correct hypovolemia and promote renal calcium excretion is the first goal of management* for hypercalcemia. Isotonic saline is recommended to maintain a urine output of 100–150 mL/hr, and this can decrease the serum calcium by 1–2 mg/dL (17).

Furosemide

Loop diuretics like furosemide can increase urinary calcium excretion, but there is no evidence that intravenous furosemide adds to the benefit of saline infusions (19), and it can be counterproductive by promoting hypovolemia. Therefore, *furosemide is recommended only to alleviate volume overload* (17,19).

TABLE 38.4 Management of Severe Hypercalcemia

Agent	Dosing Regimens and Comments
Isotonic saline	Dosing: Infuse to maintain a urine output of 100–150 mL/hr. Comment: Can reduce the serum Ca^{++} by 1–2 mg/dL.
Calcitonin	Dosing: 4 Units/kg by subQ injection every 12 hrs for 24–48 hrs. Comment: Rapid onset of action (2 hrs). Tachyphylaxis is common.
Bisphosphonates	Dosing: Zoledronate (4 mg IV over 15 min) or Pamidronate (60–90 mg IV over 4 hrs). Comment: First line drugs, but have a delayed onset of action (48 hrs), and can be nephrotoxic. Zoledronate may be more effective.
Glucocorticoids	Dosing: IV Hydrocortisone (200–400 mg daily) for 3 days, then Prednisone (10–20 mg daily) for 7 days. Comment: Most effective in patients with myeloma and lymphoma.

From References 17,18.

Calcitonin

As mentioned earlier, calcitonin lowers serum calcium by inhibiting calcium release from bone. Salmon calcitonin can be given subcutaneously in a dose of 4 Units/kg every 12 hours. The response is rapid (onset within a few hours), and the serum calcium can decrease by 1–2 mg/dL (18). However, tachyphylaxis is common, and the treatment is discontinued after 24–48 hrs.

Glucocorticoids

Glucocorticoids have several effects that can decrease the serum calcium, including decreased osteoclast activity in bone, and decreased extrarenal production of calcitriol (in lymph nodes). The glucocorticoid regimen usually begins with IV hydrocortisone (200–400 mg daily) for 3 days, followed by prednisone (10–20 mg/day) for 7 days (18). Effectiveness is most evident in patients with multiple myeloma and lymphoma (17).

Bisphosphonates

The bisphosphonates are potent inhibitors of osteoclast activity. Two drugs in this class, *zoledronate* (4 mg IV over 15 min) and *pamidronate* (90 mg IV over 2 hours) are considered first line agents in the treatment of severe hypercalcemia (17,18). Zoledronate is favored because it is easier to administer, and it may be more effective than pamidronate (17,18). Both drugs have a delayed onset of action (2–4 days), and should be started as soon as the decision to treat is made. The peak effect is at 4–7 days, and the effect lasts 1–4 weeks. These agents can be nephrotoxic, and some recommend reduced dosing when the creatinine clearance is <50 mL/min (18).

Dialysis

If necessary, hemodialysis or peritoneal dialysis can be used to remove calcium in patients with renal failure.

HYPOPHOSPHATEMIA

Inorganic phosphate (PO_4) is predominantly intracellular in location, where it participates in glycolysis and high energy phosphate (ATP) production. The normal concentration of PO_4 in plasma is shown in Table 38.1 (18).

Hypophosphatemia (serum PO_4 < 2.5 mg/dL or <0.8 mmol/L) is present in as many as 80% of ICU patients (20), and is especially common after major surgery, and in multisystem trauma and fulminant sepsis.

Predisposing Conditions

Hypophosphatemia can be the result of reduced phosphate absorption from the GI tract, increased phosphate excretion in the urine, or the transcellular movement of phosphate into cells.

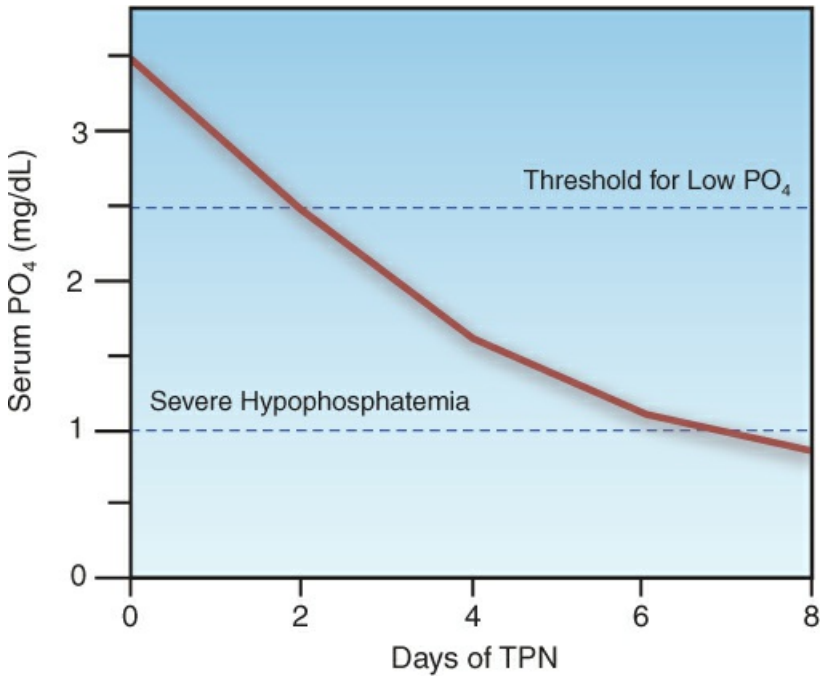

FIGURE 38.2 The effect of total parenteral nutrition (TPN) on the serum phosphate level. Data from Reference 21.

Glucose Loading

The movement of glucose into cells is accompanied by a similar movement of PO_4 into cells (presumably because PO_4 is needed for glycolysis), and this can lead to hypophosphatemia if extracellular PO_4 levels are marginal. *Glucose loading is the most common cause of hypophosphatemia in hospitalized patients* (21,22), and typically occurs with refeeding in alcoholic, malnourished, or debilitated patients. In fact, hypophosphatemia is considered a major source of *refeeding syndrome*, which can culminate in respiratory failure and cardiovascular collapse (22,23).

An example of the glucose loading effect is demonstrated in Figure 38.2, which shows the effect of total parenteral nutrition (TPN) on serum PO_4 levels (21). Note that hypophosphatemia appeared after 2 days of TPN, and reached severe levels (serum PO_4 < 1 mg/dL) after one week. TPN regimens are characteristically rich in carbohydrates (see Chapter 50), and the risk of hypophosphatemia mandates close monitoring of the serum PO_4 levels during TPN.

The glucose loading effect is also responsible for the hypophosphatemia that occurs in *diabetic ketoacidosis* (see Chapter 32). In this situation, the prolonged hyperglycemia results in an osmotic diuresis (from glycosuria) that promotes urinary PO_4 losses, and the hypophosphatemia appears when insulin is given (which drives glucose and PO_4 into cells).

Respiratory Alkalosis

Respiratory alkalosis can increase intracellular pH, and this accelerates glycolysis. The increase in glucose utilization is then accompanied by an increase in glucose and PO_4 movement into cells (24). This may be an important source of hypophosphatemia in ventilator-dependent patients, because overventilation and respiratory alkalosis are common in these patients.

Physiological Stress

Stimulation of β-adrenergic receptors can move PO_4 into cells, and this creates a risk of hypophosphatemia during periods of physiological stress (from the actions of endogenous catecholamines). This is demonstrated by the common association of hypophosphatemia with panic attacks (25).

Systemic Inflammation

There is an inverse relationship between serum PO_4 and circulating levels of inflammatory cytokines (26). Possible explanations include increased PO_4 utilization by activated neutrophils, and a transcellular shift of PO_4 caused by endogenous catecholamines.

Phosphate Binding Agents

Aluminum can form insoluble complexes with inorganic phosphates. As a result, aluminum-containing compounds such as sucralfate can impede the absorption of phosphate in the upper GI tract and promote phosphate depletion (27).

Clinical Manifestations

Hypophosphatemia is often clinically silent, even when the serum PO_4 falls to extremely low levels. In one study of patients with severe hypophosphatemia (i.e., serum $PO_4 < 1$ mg/dL), none of the patients showed evidence of harm (28). However, severe phosphate depletion creates a risk for impaired oxidative metabolism.

Oxidative Metabolism

Phosphate depletion has several effects that could impair oxidative metabolism. These are summarized below, and indicated in Figure 38.3.

. *Cardiac output:* Phosphate depletion can impair myocardial contractility and reduce cardiac output. Hypophosphatemic patients with heart failure have shown improved cardiac performance after phosphate supplementation (29).

. *Erythrocytes:* Reduction of high energy phosphate production from glycolysis in erythrocytes can reduce the deformability of red cells. This may explain why severe hypophosphatemia can be accompanied by a hemolytic anemia (30).

. *Oxyhemoglobin Dissociation:* Phosphate depletion is accompanied by depletion of 2,3 diphosphoglycerate, and this shifts the oxyhemoglobin dissociation curve to the left. When this occurs, hemoglobin is less likely to release oxygen to the tissues.

. *Energy Availability:* Phosphate depletion can reduce the availability of cellular energy by impeding the production of high-energy phosphate compounds (ATP).

Muscle Disorders

Hypophosphatemia is a reported cause of rhabdomyolysis (31) and respiratory muscle weakness (32), but the clinical significance of these associations is unclear.

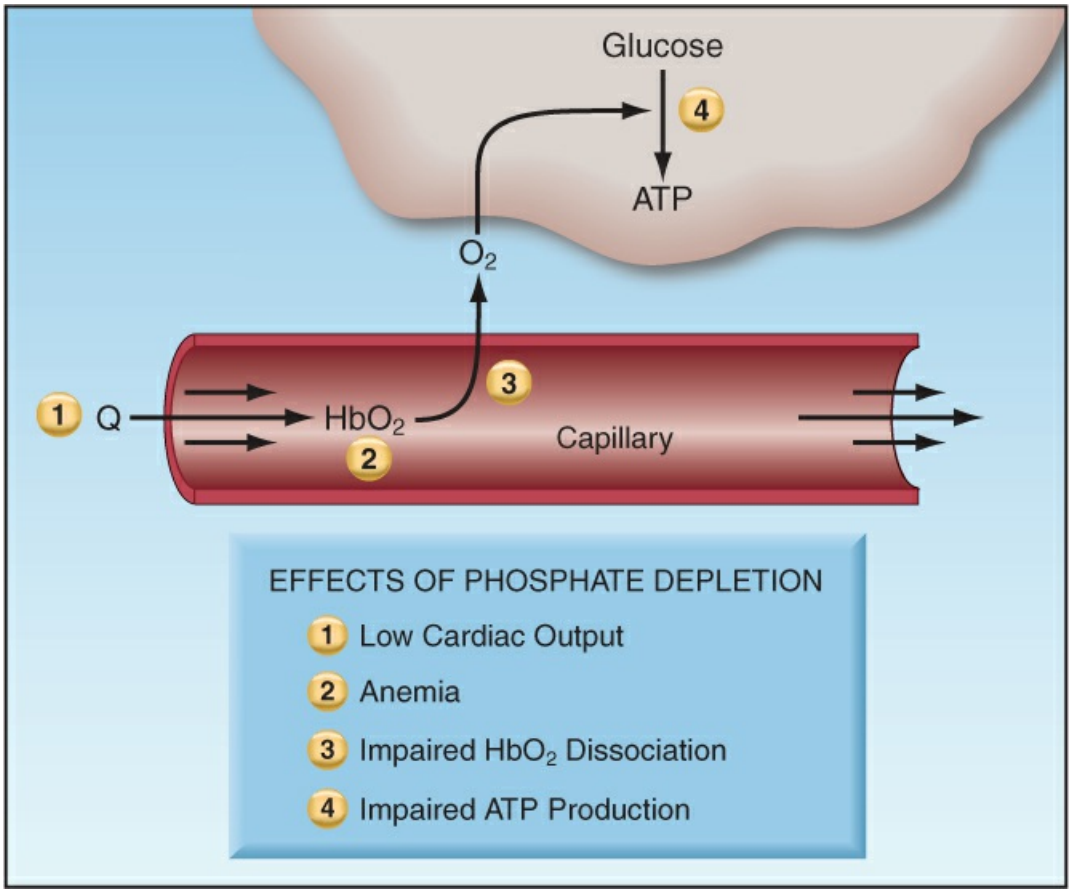

FIGURE 38.3 The effects of hypophosphatemia that threaten oxidative metabolism and cellular energy production. See text for explanation

Phosphate Replacement

Intravenous phosphate replacement is recommended for all patients with severe hypophosphatemia (i.e., serum PO_4 < 1.0 mg/dL or 0.3 mmol/L), and for patients with hypophosphatemia of any degree who also have cardiac dysfunction, respiratory failure, or rhabdomyolysis. The phosphate solutions and dosing regimen are shown in Table 38.5 (33).

TABLE 38.5 Phosphate Replacement Therapy

Solution†	PO_4 Content	Other Content
Sodium Phosphate Potassium Phosphate	93 mg (3 mmol)/mL 93 mg (3 mmol)/mL	Na^+: 4.0 mEq/L K^+: 4.3 mEq/L

PO_4 Replacement (IV) by Body Weight			
Serum PO_4 (mg/dL)	40–60 kg	61–80 kg	81–120 kg
<1	30 mmol	40 mmol	50 mmol
1–1.7	20 mmol	30 mmol	40 mmol
1.8–2.5	10 mmol	15 mmol	20 mmol

†If the plasma K^+ is ≥4 mEq/L, use sodium phosphate, and if the plasma K^+ is <4 mEq/L, use potassium phosphate.

From Reference 33

Summation

Like hypocalcemia, hypophosphatemia is common and often clinically silent, and is considered more of a general marker of illness than a pathological condition that deserves corrective action (20).

HYPERPHOSPHATEMIA

The principal cause of hyperphosphatemia in the ICU is end-stage renal disease (usually chronic, and often dialysis-dependent). Less common sources are tumor lysis syndrome and hypoparathyroidism.

Clinical Manifestations

The consequences of hyperphosphatemia include the formation of insoluble calcium–phosphate complexes (with deposition into soft tissues), and hypocalcemia (11). However, neither of these manifestations has any proven significance in ICU patients.

Management

The management of hyperphosphatemia usually involves the use of phosphate binders to reduce GI absorption of phosphate.

Phosphate Binders

Phosphate binders are separated into calcium-containing and non-calcium-containing products. Some prefer the non-calcium-containing binders because there is a daily limit of calcium intake (<800 mg) in patients with chronic kidney disease. However, there is no evidence that one type of phosphate binder is superior to the other (34). The following are examples of each type of phosphate binder.

SEVELAMER: Sevelamer is a non-calcium-containing phosphate binder that is provided as a powder, and is reconstituted in water. The dose is determined by the serum PO_4 level (35):

Serum PO_4 (mg/dL)	Dosage
5.6–7.4	800 mg TID
7.5–8.9	1,200–1,600 mg TID
>9	1,600 TID

(TID is three times daily). Sevelamer gluconate is preferred to sevelamer hydrochloride because the latter preparation can cause a metabolic acidosis (36).

CALCIUM ACETATE: Calcium acetate (PhosLo®) is available in tablets (667 mg per tab) or an oral solution (667 mg/5 mL). The initial dose is 1,334 mg (2 tabs or 10 mL) three times daily, and

this can be increased to achieve a serum PO_4 < 6 mg/dL, as long as hypercalcemia does not develop (37).

A FINAL WORD

The Normalization Heuristic

Disorders of calcium and phosphate in ICU patients are notable for the lack of apparent adverse consequences in most patients. This is especially true for hypocalcemia and hypophosphatemia, which seem to be general markers of illness rather than pathologic disorders that need corrective treatment.

The practice of correcting abnormal electrolyte values, even when there is no apparent harm, has been termed the *normalization heuristic* (38), and has two characteristic features: it is very common, and is lacking in merit. It is important to emphasize that the normal range for electrolytes is a statistically-determined domain (i.e., two standard deviations around the mean), and values outside this domain can be normal outliers, and not pathological entities that need corrective action.

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Section XII

THE ABDOMEN & PELVIS

Obscurity is painful to the mind, as well as the eye.

David Hume

Chapter 39

Liver Failure

Intellectually, we stand on an islet in the midst of an illimitable ocean of inexplicability. Our business . . . is to reclaim a little more land.

T.H. Huxley (*a*)

The management of patients with liver failure is a particular challenge because of the numerous life-supporting functions that are lost when the liver fails. These include: (*a*) the production of about 20,000 proteins, including all the coagulation factors and transport proteins in blood, (*b*) the metabolism of innumerable endogenous and exogenous substances, and (*c*) the removal of microbes that breach the mucosal barrier in the GI tract.

This chapter describes the major problems that prompt ICU admission in patients with liver failure, and includes the problems associated with both acute liver failure (with no prior history of liver disease) and decompensated cirrhosis. This is an expansive topic that is only briefly described here, and a number of clinical practice guidelines are included in the bibliography at the end of the chapter (1–5).

ACUTE LIVER FAILURE

Acute liver failure (ALF) is an abrupt and rapid deterioration in liver function that occurs *de novo*, without prior liver disease. This is an uncommon condition, as demonstrated in Figure 39.1 by the number of cases (2,614) recorded in the United States over a period of 20 years (6).

Etiologies

The conditions included in Figure 39.1 were responsible for about 80% of cases of ALF in the United States, and acetaminophen tops the list by a great margin.

Acetaminophen

Acetaminophen is the leading cause of ALF in both the United States and the United Kingdom (being responsible for 46% and 64% of cases, respectively) (6). Acetaminophen hepatotoxicity is described in detail in Chapter 52, and is only briefly reviewed here. The source of the liver injury is depletion of hepatic glutathione stores, which results in oxidative cell injury from an

acetaminophen metabolite. (Glutathione is the major intracellular antioxidant in the body, as described in Chapter 25.) The liver injury can begin as early as 12 hours after ingestion, and it peaks in 3 to 5 days (7). The laboratory abnormalities in the early stages of injury are characterized by high alanine aminotransferase (ALT) levels, with only mild increases in bilirubin (6). Acetaminophen-induced liver injury has two unfortunate features:

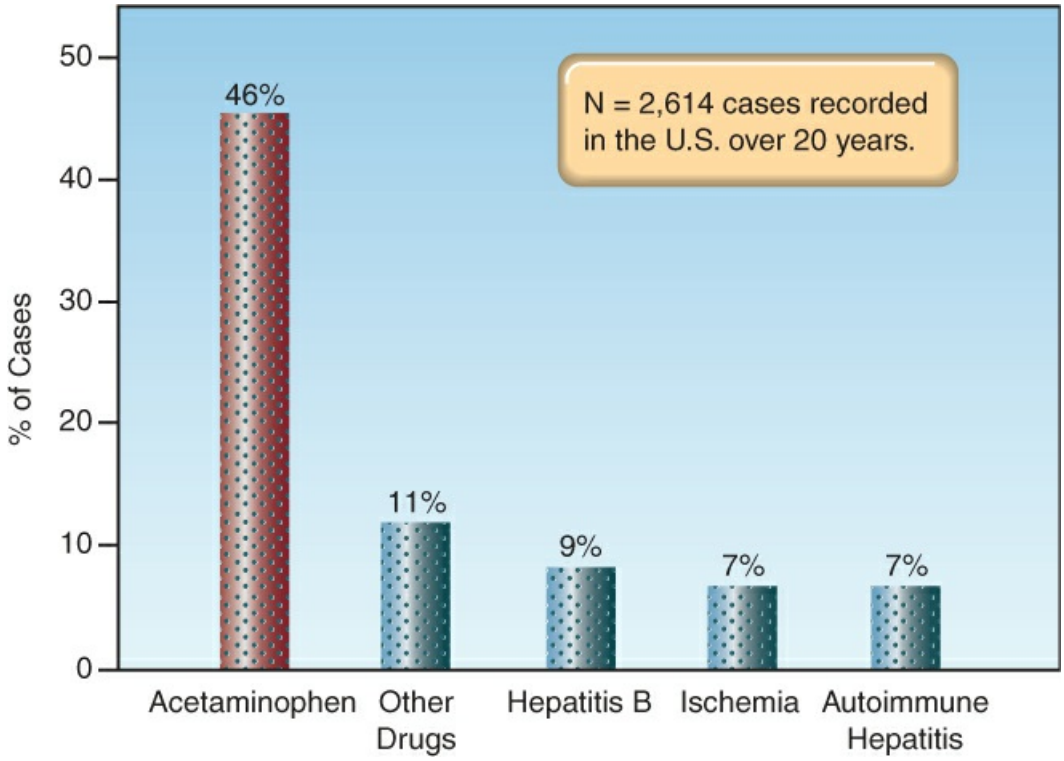

FIGURE 39.1 Causes of acute liver failure recorded by the United States Adult Acute Liver Failure Registry over the time period from Jan, 1998 to March, 2019. Adapted from Reference 6.

. About half of acetaminophen overdoses are unintentional (7), and are the result of attempts to alleviate pain. This is partly due to consumer ignorance about the potential toxicity of acetaminophen, and is partly due to the inclusion of acetaminophen in more than 600 over-the-counter products.

. Acetaminophen is undetectable in the plasma in about 50% of the cases where it causes liver injury (8). This creates a risk of missed diagnoses and poor outcomes, since the condition is treatable.

N-ACETYLCYSTEINE: The antidote for acetaminophen hepatotoxicity is N-acetylcysteine (NAC), which acts as a glutathione surrogate (see Figure 25.7). It is usually given intravenously (see Chapter 52 for the dosing regimen), and is started as soon as an acetaminophen overdose is confirmed or suspected. It is most effective when treatment is started within 10 hours of ingestion (7), and the efficacy declines with time thereafter. However, NAC is started at any time after a suspected or confirmed overdose of acetaminophen, and treatment is continued until there is evidence of improvement in liver function. About 75% of cases resolve without the need for liver transplantation (6).

The success of NAC in acetaminophen-induced ALF has led to its use in cases of ALF that are not linked to acetaminophen. Although there is no convincing evidence of benefit (9), it is considered reasonable to use NAC empirically in ALF of undetermined etiology (10).

Other Drugs

The drugs that have been reported to cause acute liver injury are listed in Table 39.1 (11). Drug-induced liver injury can be dose-related or idiosyncratic, and is more likely to occur in patients who are elderly, debilitated, or alcoholic. The idiosyncratic reactions are the most troublesome, with a survival rate of only 40% without liver transplantation (6).

TABLE 39.1 Drugs Associated with Acute Liver Failure†

Dose-Related	Idiosyncratic
Acetaminophen	Amiodarone§
Amiodarone§	Amoxicillin
Antimetabolites	Dantrolene
Antiretroviral Drugs	Halothane
Cyclosporine	Lisinopril
Statins§	Phenytoin
Valproic Acid	Statins§
	Sulfonamides

†For a more complete list, see References 6 and 11.

§Hepatic injury can be dose-related or idiosyncratic.

Ischemic Injury

Ischemic liver injury (sometimes called ischemic hepatitis), typically follows a period of systemic hypoperfusion (e.g., from hemorrhagic shock), and is characterized by very high transaminase levels (e.g., >3,000 IU/L) with only mild increases in bilirubin (<5 mg/dL) (6). This condition tends to resolve if the hypoperfusion resolves, but about 25% of cases need liver transplantation (6).

Acute Hepatitis

Autoimmune hepatitis has a more insidious onset than the other sources of ALF, and the diagnosis often rests on a clinical history of autoimmune disease, or positive serologies (e.g., antinuclear antibodies or anti-smooth muscle antibodies). About 80% of cases are in women (6), and hypergammaglobulinemia is common.

Viral hepatitis is responsible for <10% of cases of ALF in developed countries (5). Most cases are caused by the hepatitis B virus, which can be a new infection, or a latent infection that is sparked by immunosuppressive therapy. Once liver failure develops, treatment (with nucleoside analogues) is of little value (12), and survival is only 25% without liver transplantation (6).

Other Causes

Causes of ALF that are not included in Figure 39.1 include the HELLP syndrome (hemolysis, elevated liver enzymes and low platelets in pregnant and post-partum women), Budd Chiari

syndrome (hepatic vein occlusion), other viral infections (e.g., herpes simplex), and infiltrating neoplasms (6).

Clinical Features

Unlike the liver failure associated with cirrhosis, ALF is not accompanied by ascites or bleeding from esophageal varices. Instead, the clinical picture is dominated by systemic inflammation (originating from the damaged liver) with hemodynamic instability and multiorgan dysfunction (similar to inflammatory shock, as described in Chapter 17).

Hemodynamics

The hemodynamic instability in ALF is due to vasodilation, and an ineffective circulating blood volume from hypoalbuminemia (10). The management involves volume resuscitation and vasopressors if needed, and *albumin is recommended as the resuscitation fluid*, especially when the serum albumin is below 3 g/dL (2). Albumin is available as a 5% solution that has an albumin concentration of 5 g/dL (similar to the normal concentration in plasma), and about 70% of the infused solution will remain in the intravascular space (see Figure 10.1). The use of *Ringer's lactate is not advised* because it promotes hyponatremia, which will exacerbate the cerebral edema in hepatic encephalopathy.

Acute Kidney Injury

Acute kidney injury (AKI) is reported in 70% of patients with ALF, and is usually seen in patients with acetaminophen hepatotoxicity, or those with hypotension who require vasopressors (13). Renal replacement therapy is used more aggressively in ALF because it protects against hepatic encephalopathy by removing ammonia as well as excess volume (see next).

Hepatic Encephalopathy

Encephalopathy is the dominant feature of acute liver failure, and is characterized by cerebral edema (as shown in Figure 39.2).

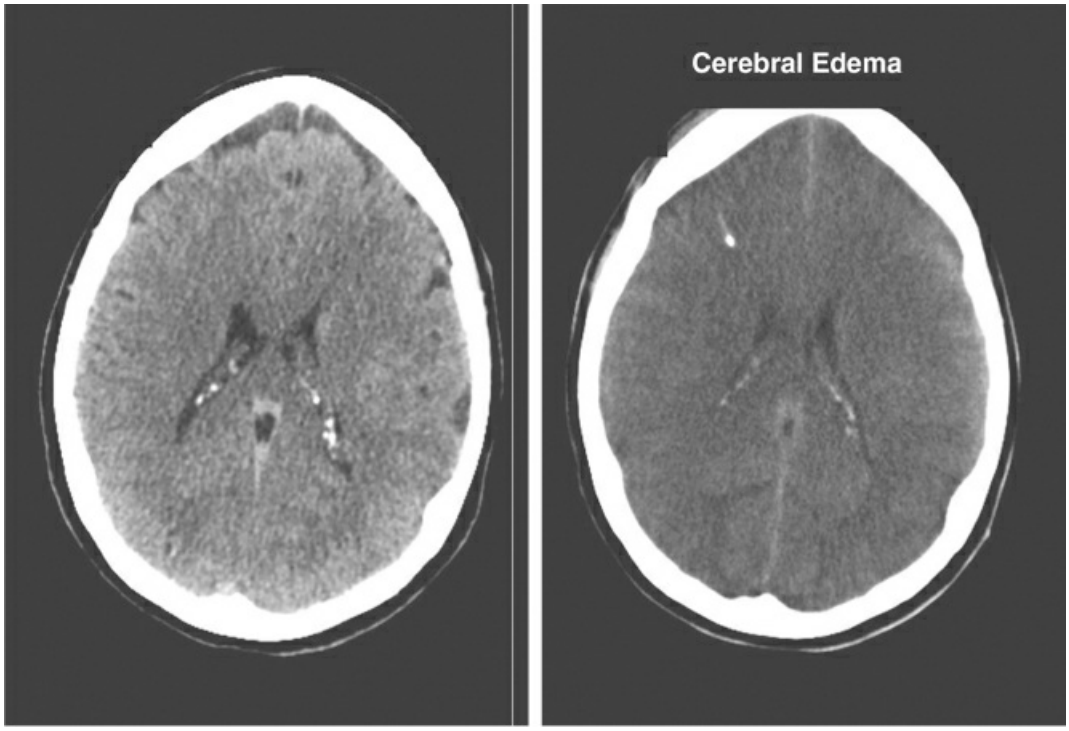

FIGURE 39.2 CT images of the head in a patient with acute liver failure, taken before (image on the left) and after (image on the right) the onset of cerebral edema. Note the effacement of sulci and loss of the grey-white interface in the image on the right. Images from Reference 6.

Pathogenesis

Ammonia has an important role in the cerebral edema that can develop in liver failure (14). Ammonia is a byproduct of protein degradation, and is produced primarily in the bowel (and to a lesser degree in skeletal muscle and kidneys). The liver plays a major role in clearing ammonia by converting it to urea via the urea cycle. This clearance mechanism is impaired or lost in liver failure, resulting in a progressive rise in ammonia levels in blood. Ammonia eventually crosses the blood-brain barrier and is taken up by astrocytes, where it is used to produce glutamine. The subsequent accumulation of glutamine then creates an osmotic force that draws water into the astrocytes and creates *a "cytotoxic" type of cerebral edema*.

Clinical Features

The clinical manifestations of hepatic encephalopathy include both cognitive and motor deficits. The cognitive changes that appear in progressive stages of hepatic encephalopathy are shown in Table 39.2 (15). Personality changes and mild disorientation are prominent in the early stages, while depressed consciousness dominates the later stages. The motor deficits can appear at any stage, and include extrapyramidal and cerebellar signs like rigidity, dysphagia, ataxia, and a flapping tremor (asterixis).

TABLE 39.2 The "West Haven" Criteria for Hepatic Encephalopathy

Grade	Features
Grade 1	• Short attention span

	• Personality change
Grade 2	• Apathy or lethargy • Disoriented to time
Grade 3	• Stuporous but responsive • Disoriented to place and time
Grade 4	• Coma

From Reference 15.

PLASMA AMMONIA LEVEL: Plasma ammonia levels are almost always elevated in patients with hepatic encephalopathy, and in many (but not all) cases, there is a correlation between the degree of elevation of the plasma ammonia and the severity of the encephalopathy (16). (This correlation occurs more frequently in ALF than in decompensated cirrhosis.) Arterial ammonia levels may be more predictive than venous levels, at least in the early stages of encephalopathy (16). *An arterial ammonia level >150 µmol/L (normal <60 µmol/L) marks an increased risk of cerebral edema* (17).

Management

The prevention and treatment of hepatic encephalopathy is aimed at reducing the ammonia burden in the central nervous system. This is done by reducing ammonia production in the bowel (e.g., with lactulose and a nonabsorbable antibiotic), and clearing ammonia from the bloodstream (with hemofiltration).

LACTULOSE: Lactulose is a disaccharide that is metabolized by "lactic acid bacteria" (e.g., *Lactobacillus acidophilus*) in the bowel (18). This promotes the formation of short-chain fatty acids, and the resulting acidification of the bowel lumen helps to eradicate ammonia-producing microbes. (The bactericidal actions of an acid pH are illustrated in Figure 4.3.) The dosing recommendations for lactulose are as follows (19):

. *Oral or Nasogastric Route:* Start with 20–30 g (30–45 mL) every hour until laxation occurs, then reduce to 20 g (30 mL) every 8 hours, and titrate to achieve 2–3 loose stools daily.

. *Retention Enema:* Mix 200 g (300 mL) with 700 mL of tap water. Administer by high rectal enema, and retain for 30–60 minutes with patient in the Trendelenburg position.

Lactulose can produce an osmotic diarrhea, and the dosage should be reduced (or temporarily halted) if diarrhea appears.

RIFAXIMIN: Rifaximin is a nonabsorbable antibiotic with a wide spectrum of activity that has proven successful in alleviating symptoms of hepatic encephalopathy when given in a dose of 400 mg three times daily for at least 10 days (20). Although effective when used alone, it is usually combined with lactulose.

HEMOFILTRATION: Continuous venovenous hemofiltration (CVVH) can lower plasma ammonia levels and improve outcomes in patients with ALF (21), especially with continued use (20). At

the present time, CVVH is considered superior to lactulose or rifaximin for patients with ALF and hepatic encephalopathy, and should be considered in the following situations: (*a*) persistent oliguria, (*b*) plasma ammonia level >150 μmol/L, and (*c*) evidence of cerebral edema, regardless of the serum creatinine (5). CVVH should be started as soon as possible, as its effectiveness is time-dependent (22).

Liver Transplantation

Liver transplantation is the definitive treatment for ALF, and has reduced the mortality rate from 80% to 33% (6). There are several scoring systems that are used to identify who will benefit from transplantation, but this is the domain of the transplant specialist, who should be consulted for any patient with ALF who develops progressive hepatic encephalopathy.

ACUTE-ON-CHRONIC LIVER FAILURE

Most admissions to the ICU for liver failure involve patients with chronic liver disease (usually cirrhosis) who experience an abrupt deterioration in liver function. This *acute-on-chronic liver failure* is often complicated by: (*a*) bleeding from gastroesophageal varices, (*b*) hepatic encephalopathy, (*c*) infections, and (*d*) acute kidney injury. This section describes each of these complications, with the exception of hepatic encephalopathy, which is described in the previous section.

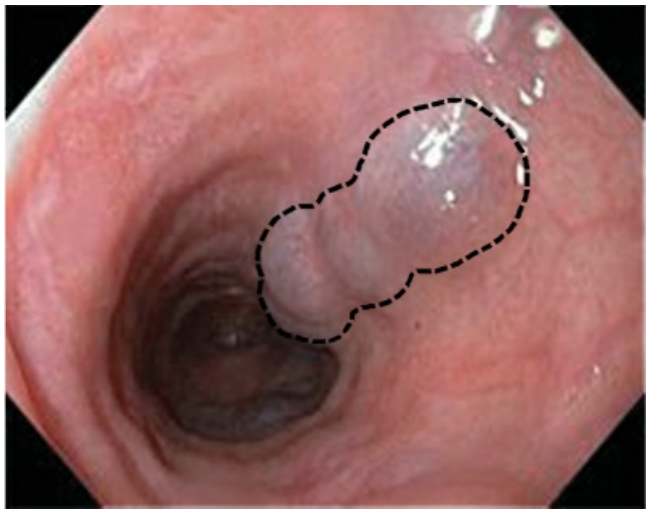

FIGURE 39.3 Endoscopic view of esophageal varices, which appear as engorged submucosal veins (outlined by the dotted line). Image courtesy of S. Bhimji, MD; digitally retouched.

Variceal Hemorrhage

Gastroesophageal varices are engorged submucosal veins that appear as a consequence of portal hypertension (see Figure 39.3). Acute bleeding from ruptured varices is one of the more life-threatening complications of advanced liver disease.

Management

The management of acute variceal bleeding, which is outlined in Table 39.3 (4), involves source

control (with endoscopy), resuscitation (with fluids and blood products), vasoactive therapy (with octreotide), and prophylactic measures (with antibiotics). Intubation may also be necessary in patients with altered mentation.

TABLE 39.3 The Management of Acute Variceal Bleeding

Component	Recommendations
Endoscopy	• Perform within 12 hrs.
Volume Resuscitation	• Maintain MAP of 65 mm Hg. • Use 5% albumin as a resuscitation fluid if serum albumin <3 g/dL. • Avoid hypotonic fluids.
Blood Products	• Transfuse RBCs, plasma, and platelets in a 1:1:1 ratio. • Use a target Hb of 7 g/dL. • Use thromboelastography to guide hemostatic therapy (see Table 15.1).
Splanchnic Vasoconstrictor	• Octreotide: 50 µg as IV bolus, then infuse at 50 µg/hr for 2–5 days.
Antibiotic Prophylaxis	• Ceftriaxone, 1 g IV daily for 5–7 days. • First dose before endoscopy.

From the guidelines in References 1 and 4.

Endoscopy is recommended within 12 hours of presentation (1,4), both to identify the source of the bleeding (which has prognostic value) and to clip or band the bleeding varix. The resuscitation with asanguinous fluids and blood products is the same as described for hemorrhagic shock in Chapter 15, with the following exceptions:

. Albumin is recommended as a resuscitation fluid, especially when the serum albumin is less than 3 g/dL (2). The 5% albumin solution has an albumin concentration of 5 g/dL, which is close to the normal albumin concentration in plasma, and about 70% of the infused volume will expand the plasma volume.

. Hypotonic fluids like Ringer's lactate are not recommended because they add to the risk of cerebral edema (which is responsible for hepatic encephalopathy).

. The INR is not a valid measure of bleeding risk in patients with cirrhosis (4), and thromboelastography (described in Chapter 15) is recommended to guide hemostatic therapy (1).

The management of variceal bleeding also includes a splanchnic vasoconstrictor like *octreotide*, a somatostatin analogue that is started as soon as possible, using the dosing regimen in Table 39.3. Prophylactic antibiotics should also be started as soon as possible, and *ceftriaxone* (2 grams daily) is recommended in most guidelines (2,4). (*Note:* This recommendation assumes that resistant microbes are not prevalent in your ICU.)

Refractory Bleeding

Variceal bleeding is refractory to endoscopy and optimal medical management in about 20% of

cases (4). In this situation, a transesophageal portosystemic shunt (TIPS) procedure should be considered. TIPS is a noninvasive method that creates a shunt between the portal and hepatic veins, thereby alleviating the portal venous hypertension that creates varices. Unfortunately, the TIPS procedure trades one problem for another, as bypassing the liver increases the risk of hepatic encephalopathy.

Spontaneous Bacterial Peritonitis

About one-third of patients with decompensated cirrhosis have a bacterial infection, and the most common infection is *spontaneous bacterial peritonitis* (SBP), which is an infection of ascitic fluid without a primary site of infection in the abdomen (5). The source of this infection is the "translocation" of enteric pathogens across the bowel mucosa. SBP occurs only in patients with cirrhosis and ascites, because cirrhosis impairs the normal function of the liver to eradicate microbes that translocate across the bowel wall.

About 50% of cases of SBP are community-acquired, while 25% are classified as "healthcare-associated" (i.e., the patient has had contact with a healthcare facility within 90 days), and the remaining 25% are nosocomial (23). A single organism is isolated in most cases of SBP, and the most common isolates are gram-negative organisms (especially *Escherichia coli* and *Klebsiella pneumoniae*) with gram-positive organisms (usually staphylococci and enterococci) a distant second (23). Resistant organisms are isolated in 35% of cases worldwide, but the prevalence is much lower (16%) in the United States (23).

Diagnosis

SBP can present with fever, abdominal pain, and rebound tenderness, but it is asymptomatic in one-third of cases (24). A paracentesis is required for the diagnosis, and *an absolute neutrophil count >250/mm^3 in ascitic fluid secures the diagnosis, regardless of the culture result* (5). An organism is isolated in about 60% of cases (23). A positive culture without the required neutrophil count in ascitic fluid is not sufficient for the diagnosis of SBP (5). (In this situation, a repeat paracentesis is wise.)

SBP should be suspected in all patients with decompensated cirrhosis and liver failure who are admitted to the ICU, or who experience a sudden deterioration while in the hospital (5). A paracentesis should be performed when SBP is suspected, and the fluid sent for cell count and culture. For optimal culture results, the ascitic fluid should be added to blood culture bottles (aerobic and anaerobic) at the bedside.

Antibiotic Therapy

Antibiotic therapy is started in all cases when the absolute neutrophil count is >250/mm^3 (before the culture results are available). The choice of antibiotic is determined by the place of origin of the infection, and the prevalence of resistant organisms in your ICU. This is shown in the algorithm in Figure 39.4 (25), which can be summarized as follows:

. Resistant organisms are unlikely in community-acquired SBP (23), and a third generation cephalosporin (e.g., cefotaxime or ceftriaxone) is generally recommended.

. Resistant organisms are typically isolated in nosocomial cases of SBP, and less frequently in healthcare-associated infections (23). (*Note:* A nosocomial infection is one that appears after

48 hrs in the hospital, while a healthcare-associated infection is one that appears within 48 hrs after admission in a patient who has had contact with a healthcare facility in the last 90 days.)

a. If a resistant infection is possible, a carbapenem (e.g., meropenem 1 gram every 8 hours) is recommended (25), with vancomycin added if methicillin-resistant *Staphylococcus aureus* is a potential offender, or daptomycin if vancomycin-resistant enterococci are suspected.
b. If a resistant organism is unlikely, broad-spectrum coverage for enteric pathogens (e.g., with piperacillin-tazobactam) is sufficient.

Antibiotics should be continued for at least 7 days, regardless of the culture results. The response to antibiotics can be assessed by a repeat paracentesis after 48 hours: i.e., a favorable response is defined as a ≥25% decrease in the neutrophil count (5).

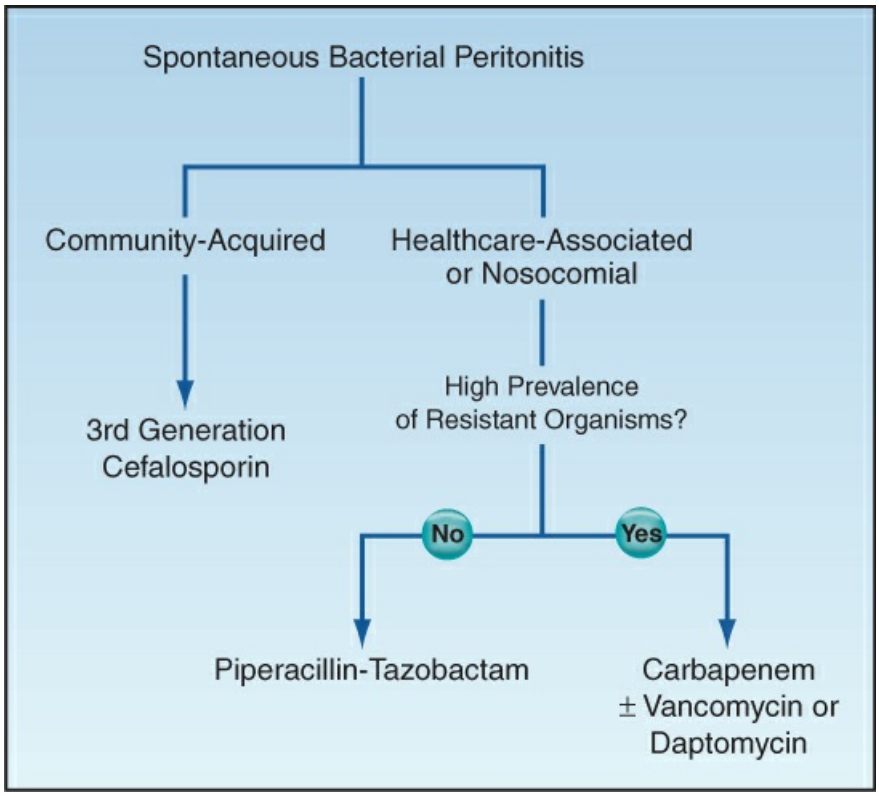

FIGURE 39.4 Algorithm for the empiric antibiotic treatment of spontaneous bacterial peritonitis. From Reference 25.

Albumin Infusions

Infusions of albumin have been shown to improve survival in SBP (26,27). This was originally attributed to an improvement in renal function (27), because acute kidney injury develops in 30% of patients with SBP (25), and this increases the mortality rate considerably (28). However, more recent studies have shown that the survival benefit of albumin is independent of the serum creatinine (26). The recommended albumin regimen is 1.5 g/kg on day one, followed by 1 g/kg on day 3 (5). The 25% albumin solution (25 g/100 mL) is recommended, to limit the infusion volume.

Hepatorenal Syndrome

Acute kidney injury (AKI) is reported in as many as 50% of patients with decompensated cirrhosis (5). The hepatorenal syndrome (HRS) is a type of "functional AKI" that occurs without intrinsic renal disease, and its appearance heralds a poor prognosis.

Pathogenesis

HRS is the result of hemodynamic alterations in the splanchnic and renal circulations. Cirrhosis is associated with splanchnic vasodilation, and the neurohumoral (renin system) response to this vasodilation results in vasoconstriction in other organs, including the kidneys. The renal vasoconstriction creates a situation where the glomerular filtration rate is vulnerable to small decrements in cardiac output. Sepsis enhances the vasodilation from cirrhosis, and HRS is more frequent when cirrhosis is accompanied by sepsis.

Diagnosis

The diagnostic criteria for HRS are listed in Table 39.4 (29). The criteria include evidence of AKI (i.e., an increase in serum creatinine ≥0.3 mg/dL within 48 hrs) with no other apparent cause (i.e., no circulatory shock or nephrotoxic drugs), and no evidence of intrinsic kidney disease. Urinary indices in HRS are similar to "prerenal" indices (i.e., low sodium and high osmolarity), and these could differentiate HRS from acute tubular necrosis.

TABLE 39.4 Diagnosis and Management of Hepatorenal Syndrome

I. *Diagnostic Criteria:*
1. Cirrhosis with ascites.
2. Increase in SCr of ≥0.3 mg/dL within 48 hrs, or SCr ≥1.5 times baseline.
3. No response to diuretic withdrawal and 2 days of fluid challenges with albumin (1 g/kg/day).
4. No evidence of shock, and no recent use of nephrotoxic drugs.
5. No signs of structural kidney injury:
   a. Absence of proteinuria (>500 mg/day).
   b. Absence of hematuria (>50 RBC's per high power field).
   c. Normal findings on renal ultrasound.

II. *Management:*
1. Albumin (25%): 20–40 g daily.
2. Splanchnic vasoconstriction with one of the following:
   a. Terlipressin: 1 mg IV every 4–6 hrs, or infuse at 84 µg/hr (2 mg/day).
   b. Norepinephrine: 5–40 µg/min by continuous infusion.
   c. Octreotide (100–200 µg subQ) plus midodrine (7.5–15 mg PO) three times daily.

From Reference 29.

Management

The management of HRS is included in Table 39.4. Daily doses of albumin are recommended at a dose of 20–40 grams daily, which should be given as a 25% albumin solution (25 grams per 100 mL) to limit the volume infused. The benefits of albumin may not be related to volume, as albumin is also an antioxidant, and has immunomodulating effects (30).

The mainstay of treatment for HRS is to promote splanchnic vasoconstriction and reverse the hemodynamic changes that precipitate the condition. The drug of choice for this is *terlipressin*, a synthetic vasopressin analogue that acts primarily as a splanchnic vasoconstrictor. Clinical studies have shown that terlipressin improves renal function in HRS (31,32), but it does not improve survival or reduce the need for liver transplantation (32). Side effects of terlipressin include abdominal pain, diarrhea, pulmonary edema (hydrostatic), and ischemic events. The drug was approved for use in the United States in 2022.

Alternatives to terlipressin include *norepinephrine*, and the combination of *midodrine and octreotide* (33). (See Table 39.4 for dosing recommendations.) Norepinephrine has been equivalent to terlipressin in clinical trials (34), but the experience is limited, while midodrine plus octreotide is inferior to terlipressin (35), and is limited to use in countries where terlipressin is not available.

Increased Abdominal Pressure

Increased intra-abdominal pressure is an overlooked cause of AKI in critically ill patients (36), as described in Chapter 34, and it is possible that it could also promote HRS. This is supported by a study showing that large-volume paracentesis (i.e., removal of ≥4 liters of fluid) improved renal function in patients with tense ascites and HRS (37). Therefore, measurement of intra-abdominal pressure is advised for all patients with tense ascites and HRS (see Chapter 34 for the method of measuring intra-abdominal pressure), and large-volume paracentesis is encouraged if the abdominal pressure exceeds 12 cm H_2O (29). However, careful hemodynamic monitoring is needed after large-volume paracentesis, to avoid hemodynamic compromise.

Liver Transplantation

Liver transplantation is the definitive treatment for HRS, and a consultation for liver transplantation should be obtained whenever HRS is diagnosed.

A FINAL WORD

The Liver & Bowel Sepsis

One of the recurring themes in this book is the importance of the bowel as a source of systemic infection and inflammation in critically ill patients (see Chapters 4 and 41). Much of the attention in this area is directed at the breakdown of the mucosal barrier in the bowel, but there is a second line of defense in the event of mucosal breakdown. This is illustrated by the occurrence of spontaneous bacterial peritonitis in patients with liver failure; an infection that is caused by enteric pathogens that escape across the bowel mucosa. This infection demonstrates the importance of the liver as a second line of defense against microbes that breach the mucosal barrier in the bowel. In fact, about three-quarters of the reticuloendothelial system is located in the abdomen (mostly represented by the liver), where it is positioned to protect against the systemic spread of enteric pathogens.

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Chapter 40

Acute Pancreatitis

Medicine cures the man who is fated not to die.

Chinese Proverb

Acute pancreatitis is cited as one of the leading abdominal disorders that requires hospitalization (1), but most cases are not severe enough to warrant ICU admission. However, the cases that do require ICU admission are often (or quickly become) the sickest patients in the ICU.

This chapter describes the clinical features and management of acute pancreatitis, with emphasis on the severe cases that require ICU-level care. Management of severe pancreatits is challenging, because there is no specific treatment (other than removing any predisposing condition), and the overall mortality rate (about 25%) has not changed over the past two decades (2).

PATHOGENESIS & PRESENTATION

The pancreas houses two types of cells: (*a*) "islet" cells that have an endocrine function, and secrete insulin, glucagon, and somatostatin, and (*b*) "acinar" cells that have an exocrine function, and secrete digestive enzymes such as amylase, lipase, and trypsin. Acute pancreatitis is an inflammatory process that primarily affects the acinar (exocrine) cells. Disruption of these cells releases digestive enzymes, and proteolytic enzymes like trypsin can aggravate the pancreatic injury and promote "autodigestion" of the pancreas. The pancreatic injury triggers a systemic inflammatory response, which can lead to inflammatory injury in other organs, culminating in multiorgan failure.

Etiologies

The causes of acute pancreatitis are listed in Table 40.1. About three-quarters of the cases are the result of gallstones, alcohol abuse, or are idiopathic (1,3), while the other causes that deserve mention are hypertriglyceridemia (4,5), drugs (6), and infections (7).

Hypertriglyceridemia

Severe hypertriglyceridemia (serum triglyceride levels >1,000 mg/dL) is responsible for up to

7% of cases of acute pancreatitis (4), and the frequency of cases has increased considerably in recent years (5). Several mechanisms may be involved, but one of the major ones is the release of polyunsaturated fatty acids (PUFA) from triglycerides, since PUFAs are highly oxidizable, and are capable of inciting an inflammatory response. (*Note:* The oxidation of PUFAs in food products is responsible for "rancidity".)

The pancreatitis from hypertriglyceridemia is more severe than other types of pancreatitis, and is associated with a greater degree of systemic inflammation and extrapancreatic organ injury (4). Fortunately, there is an effective treatment, which is described later in the chapter.

TABLE 40.1 Etiologies of Acute Pancreatitis

More Common†	Less Common
Gallstones (21–33%)	Abdominal Trauma
Alcohol (16–27%)	Hypercalcemia
Idiopathic (10–15%)	Infections
Hypertriglyceridemia (2–7%)	Pregnancy
Drugs (3–4%)	Vasculitis

†Reported prevalence indicated in parentheses.

Drugs

At least 36 drugs have been implicated as a causative factor in acute pancreatitis (1,6), but many of the cases are idiosyncratic reactions in case reports. The most frequently reported drugs are hydrochlorothiazide, azathioprine, and doxycycline (6), while the other implicated drugs include (in alphabetical order) acetaminophen, enalapril, furosemide, metronidazole, procainamide, trimethoprim-sulfamethoxazole, and valproic acid (1,6).

Infections

A variety of infectious agents can cause pancreatitis (7), including viruses (HIV, cytomegalovirus, varicella-zoster, herpes simplex, and hepatitis B), bacteria (Mycoplasma, Legionella, Leptospira, and Salmonella), fungi (Aspergillus) and parasites (Toxoplasma, Cryptosporidium). Suspicion of an infectious agent is based on the presence of other manifestations of the infection.

General Features

The general features of acute pancreatitis are summarized in Table 40.2. This is the revised Atlanta classification for acute pancreatitis (8), and it has three components: (*a*) a classification based on morphology, (*b*) diagnostic criteria, and (*c*) a severity of illness classification. Each of these is described next.

Morphology

There are two types of acute pancreatitis, based on the presence or absence of pancreatic necrosis.

. *Edematous pancreatitis* is characterized by diffuse inflammation of the pancreas, with no

evidence of pancreatic necrosis. This is the most common type of pancreatitis, and the clinical presentation is typically mild and self-limited, with no involvement of other organs (1,2).

. *Necrotizing pancreatitis* is characterized by areas of necrotic destruction in the pancreas, which can extend into the peripancreatic tissues. This condition can be complicated by local infection and extrapancreatric organ injury. The incidence of this type of pancreatitis varies in different reports, from as low as 5% (8) to as high as 40% (4).

TABLE 40.2 Classification of Acute Pancreatitis†

Feature	Definitions or Criteria
Morphology	1. Edematous Pancreatitis 2. Necrotizing Pancreatitis
Diagnostic Criteria	Any 2 of the following: 1. Characteristic abdominal pain 2. Serum amylase or lipase >3 times upper limit of normal 3. Characteristic imaging
Severity of Illness:	
A. Mild	A. No organ failure, and no local or systemic complications
B. Moderately Severe	B. Transient organ failure (<48 hrs), or local or systemic complications without persistent organ failure
C. Severe	C. Persistent organ failure (>48 hrs), single or multiple

†The revised Atlanta classification, from Reference 8.

Diagnostic Criteria

The diagnosis of acute pancreatitis requires two of the following: (*a*) abdominal pain that is characteristic of acute pancreatitis, (*b*) an increase in serum amylase or lipase levels to three times the normal range, and (*c*) a contrast enhanced CT scan (or MRI) showing edema or necrotic lesions in the pancreas.

Pancreatic Enzymes

Although no distinction is made between amylase and lipase in the diagnostic criteria, *lipase should be favored over amylase* for the following reasons:

. An increase in serum lipase to three times normal has a greater specificity for acute pancreatitis than a similar increase in serum amylase (9).

. The elevation in lipase occurs earlier than the elevation in amylase (4–8 hrs vs. 6–12 hrs, respectively), and it lasts much longer (i.e., 8–14 days for lipase, versus 3–5 days for amylase) (9).

. Monitoring the lipase level alone has the same diagnostic accuracy as monitoring both (amylase and lipase) levels (9).

The combination of abdominal pain and increased pancreatic enzymes is diagnostic in about 75–80% of cases of acute pancreatitis (1), but imaging studies are a valued addition (see next).

Imaging

CT scans of the abdomen (contrast-enhanced) are often included in the diagnostic evaluation of pancreatitis because they can identify the type of pancreatitis (edematous vs. necrotizing) and reveal localized complications (e.g., infection). Figure 40.1 shows a contrast-enhanced CT image of edematous pancreatitis. The pancreas is thickened and enhances completely, and the border of the pancreas is blurred, which is characteristic of pancreatic edema. Compare this with the image in Figure 40.2, which shows a large area in the pancreas that is not contrast-enhanced. This represents pancreatic necrosis, and identifies the condition as necrotizing pancreatitis. Pancreatic necrosis may not appear for the first week after the onset of symptoms (1), so repeat imaging is advised in patients with persistent symptoms or severe pancreatitis.

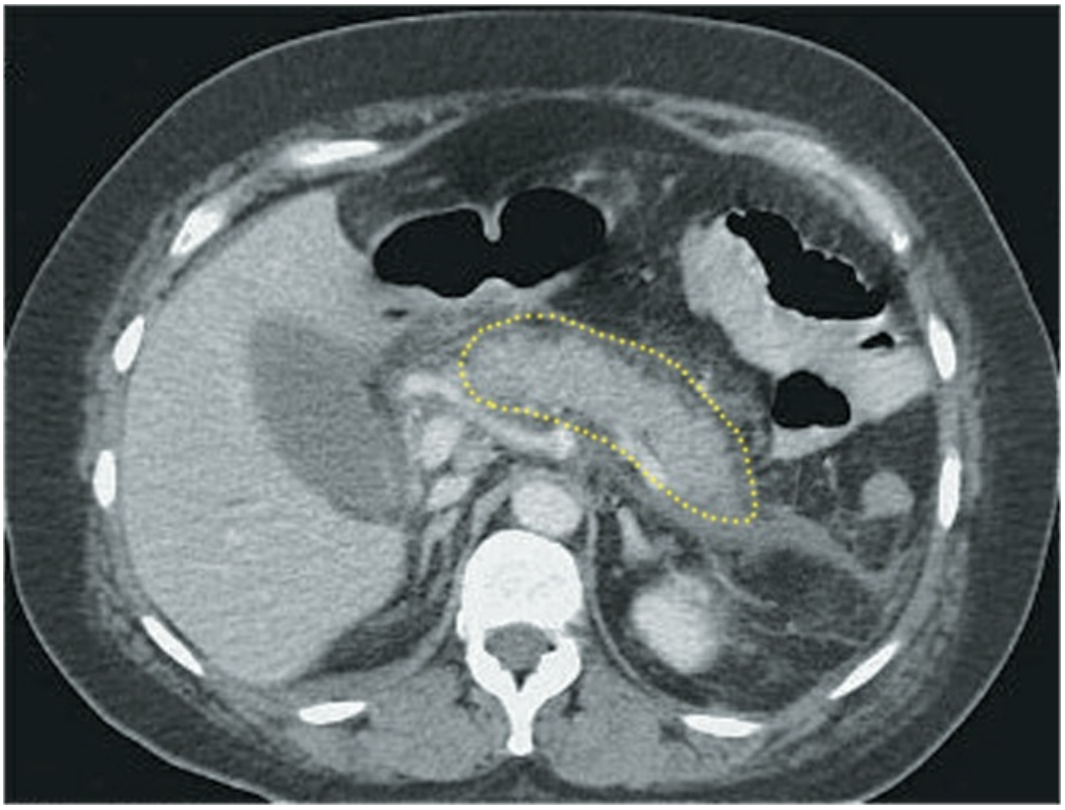

FIGURE 40.1 Contrast-enhanced CT image showing edematous pancreatitis. The pancreas (outlined by the dotted line) is enlarged and enhances completely. There is also blurring of the pancreatic border, which is characteristic of edema formation.

When IV contrast cannot be administered (e.g., because of a dye allergy), CT imaging is less likely to distinguish between edematous and necrotizing pancreatitis. In this situation, magnetic resonance imaging (MRI) is a suitable alternative.

Severity of Disease

The revised Atlanta classification of acute pancreatitis includes three categories for severity of disease, based on the presence or absence of complications, and extrapancreatic organ failure (see Table 40.2). About 50% of cases are classified as *mild disease* (symptoms self-limited, and no evidence of complications or organ failure), while the remaining 50% are equally divided

between *moderately severe disease* (transient organ failure, resolves in less than 48 hours) and *severe disease* (organ failure persists for longer than 48 hours) (10). The mortality in acute pancreatitis is mostly limited to patients with severe disease, and is about 20–25% (1,2). *Pancreatic enzymes and CT images have a poor correlation with the severity of illness.*

The extrapancreatic organ involvement in acute pancreatitis is related to the systemic inflammatory response, and can involve single or multiple organs. The organs typically involved are the lungs (i.e., acute respiratory distress syndrome), the kidneys (acute kidney injury), and the circulatory system (hypotension and circulatory shock). This organ involvement may not appear in the early stages of illness.

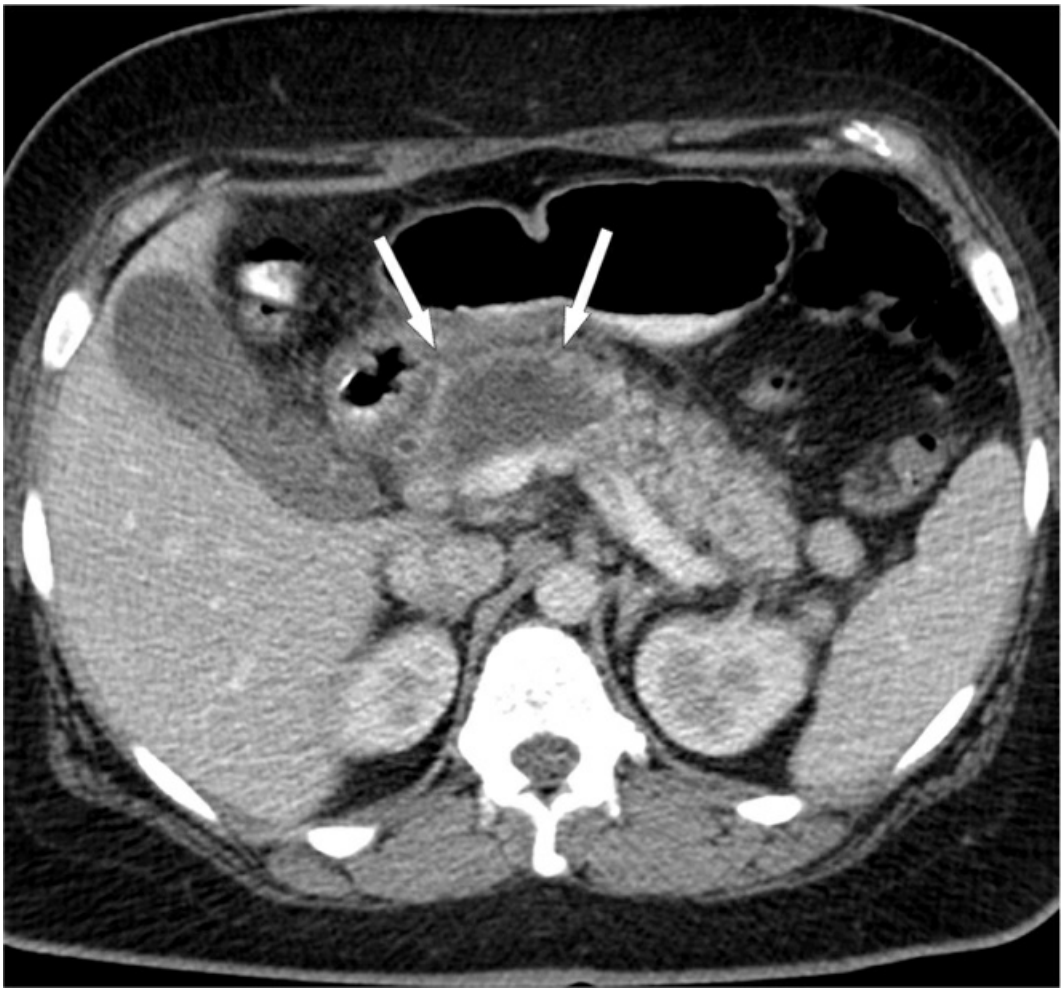

FIGURE 40.2 Contrast-enhanced CT image showing necrotizing pancreatitis. The area that is not contrast-enhanced (indicated by the arrows) represents necrosis in the neck and body of the pancreas. Image from Reference 8.

Biliary Evaluation

Since gallstones are the leading cause of acute pancreatitis, an evaluation of the gall bladder and biliary tree is advised in all cases of confirmed acute pancreatitis. Contrast-enhanced CT images may suffice for this evaluation, but in cases where a CT scan is unavailable or inconclusive, bedside ultrasonography is recommended.

MANAGEMENT

Management in the ICU is primarily for patients with moderately severe or severe disease, and mostly involves supportive care, especially with fluids and nutrition.

Fluid Management

Severe pancreatitis is associated with loss of intravascular fluid through leaky systemic capillaries, and the resulting hypovolemia can produce additional pancreatic necrosis. For this reason, attention to volume resuscitation is recommended early in the course of severe pancreatitis. The following fluid regimen is recommended:

. Ringer's lactate (RL) is the recommended fluid, based on evidence of improved outcomes with RL compared to isotonic saline (11,12). However, since RL contains calcium, it should not be used in hypercalcemia-related pancreatitis.

. Start with a bolus infusion of 10 mL/kg in patients with hypovolemia, and follow with a continuous infusion of 1.5 mL/kg per hour (13). Avoid the bolus infusion if there is no evidence of hypovolemia.

. *Caution:* More aggressive volume infusion (i.e., bolus of 20 mL/kg, and a rate of 3 mL/kg/hr) promotes fluid overload, and does not improve outcomes (13).

. The goal of fluid management is to maintain a mean arterial pressure ≥65 mm Hg, and a urine output ≥0.5 mL/kg per hour.

Vasopressors

As always, vasopressors are advised if fluid therapy does not achieve the desired blood pressure. There are no official recommendations regarding vasopressor therapy in severe pancreatitis, but norepinephrine is an appropriate choice. All vasoconstrictor drugs can reduce splanchnic blood flow (especially phenylephrine), which could promote pancreatic necrosis, so careful titration of infusion rates (and avoidance of phenylephrine) is advised.

Nutrition

Nutrition should be started early (within 48 hours after the onset of illness) using an oral diet (if tolerated) or enteral tube feedings (1,14). Parenteral nutrition is reserved for cases where enteral feeding is not tolerated (e.g., from an ileus).

Enteral Nutrition

The preference for enteral nutrition is based on the ability of oral feeding to exert a trophic effect on the bowel mucosa. This helps to maintain the integrity of the bowel mucosa and reduce the risk of bacterial translocation across the bowel wall, which is considered the major source of pancreatic infections (15). Clinical studies have shown that *enteral nutrition is associated with fewer infections, less multiorgan failure, and a lower mortality rate than total parenteral nutrition* in patients with severe pancreatitis (16).

When enteral tube feedings are used, it is unclear if gastric or jejunal feeding is optimal (17). Based on evidence that nasogastric feeding produces no apparent harm in severe pancreatitis (18), it is reasonable to start with nasogastric feeding. Elemental feeding formulas (which are

low in fat) should be preferred.

Abdominal Complications

Local complications of pancreatitis include infection, pseudocyst formation, and abdominal compartment syndrome.

Pancreatic Infection

About one-third of patients with necrotizing pancreatitis develop an infection in the necrotic areas of the pancreas, which typically appears 7–10 days after the onset of illness (19). Infection may be heralded by persistent or recurrent fever and leukocytosis, but these findings are also common in necrotic pancreatitis without infection. A contrast-enhanced CT image can reveal probable infection by the presence of gas bubbles, as shown in Figure 40.3.

If infection is suspected, antibiotic therapy should be started, with coverage for gram-negative enteric pathogens. (*Note:* Prophylactic antibiotics do not reduce the incidence of pancreatic infections, and are not recommended (20).) However, these infections are difficult to treat with antibiotics, and CT-guided drainage may be necessary. There is some debate about the timing of drainage, but there is evidence that early drainage produces better results than delayed drainage (21). If noninvasive drainage is not successful, then surgical debridement (necrosectomy) may be necessary.

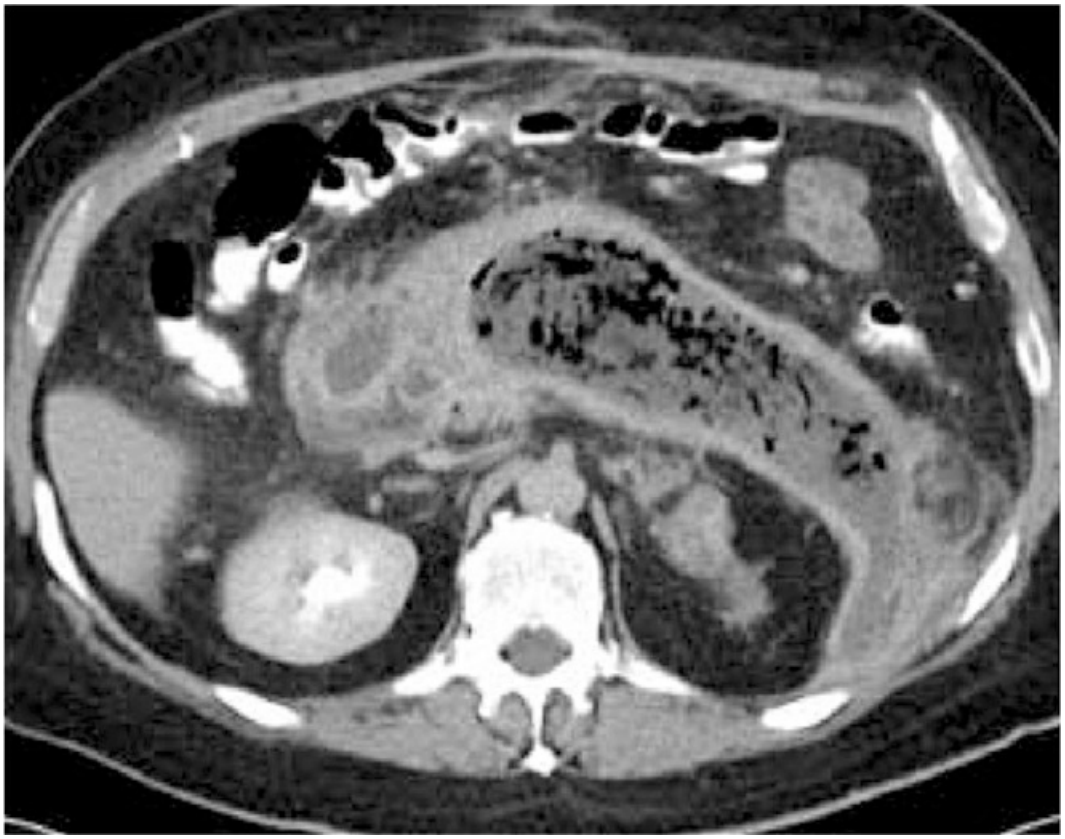

FIGURE 40.3 Contrast-enhanced CT image showing extensive necrosis of the pancreas with numerous gas bubbles, indicating infection.

Abdominal Compartment Syndrome

There are several sources of increased intra-abdominal pressure in severe pancreatitis, including peripancreatic fluid collections, ascites, and edema of the bowel wall (from aggressive volume infusion). An increase in intra-abdominal pressure (>12 cm H_2O) has been reported in 55% of patients with severe pancreatitis (22), and pressures that exceed 20 cm H_2O can cause oliguria (as described in Chapter 34). Therefore, an abdominal pressure measurement is recommended for any patient with severe pancreatitis complicated by oliguria.

Specific Therapies

The following management is specific to the cause of the pancreatitis.

Hypertriglyceridemia

The pancreatitis associated with hypertriglyceridemia can be treated with insulin, which acts on lipoprotein lipase to reduce serum triglyceride levels (4). An intravenous infusion of insulin (0.1–0.4 Units/kg/hr) can reduce triglyceride levels by 85–90% in 24 hours if combined with fasting (23). The goal of treatment in acute pancreatitis is a serum triglyceride below 500 mg/dL (4). A 5–10% dextrose infusion is advised during the insulin infusion, along with careful monitoring of serum glucose levels. Once the pancreatitis has been successfully managed, continued treatment with lipid-lowering drugs like gemfibrozil or fenofibric acid may be needed to keep triglyceride levels below 500 mg/dL (4).

Gallstone Pancreatitis

When acute pancreatitis is associated with gallstones, endoscopic retrograde cholangio-pancreatography (ERCP) with sphincterotomy is indicated if there is evidence of biliary obstruction (e.g., by ultrasound). Cholecystectomy can be performed during the initial hospitalization for mild pancreatitis, but it is delayed (4–6 weeks) after an episode of severe pancreatitis.

A FINAL WORD

Alcohol & Pancreatitis (?)

Although alcohol is widely regarded as a major source of pancreatitis, the strong link between alcohol and pancreatitis was made at a time when the diagnosis of pancreatitis was based solely on elevation of the serum amylase. The problem is that amylase is also secreted by the parotid glands, and alcohol stimulates the release of salivary amylase. In fact, *hyperamylasemia of salivary origin is reported in 40% of cases of acute alcohol intoxication* (6). It is thus possible that elevations of salivary amylase created the strong association of alcohol abuse and pancreatitis.

There are about 30 million alcoholics in the United States (24), and the number of hospital admissions for pancreatitis is 275,000 per year (25), or about 69,000 per year if you assume that 25% of cases of acute pancreatitis are caused by alcohol. This means that less than 1% (0.2%) of alcoholics develop acute pancreatitis each year, which is not a very strong association.

Why is this important? Because, whenever a patient with acute pancreatitis has a history of alcohol abuse, no efforts are made to find another cause of the illness. It seems wise not to continue this behavior.

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Chapter 41

Abdominal Infections in the ICU

My dear Watson, you see, but you do not observe.

Arthur Conan Doyle (*a*)

The concept of the bowel as noxious reservoir first appeared in the early years of the twentieth century, when a Scottish surgeon named William Arbuthnot-Lane began performing total colectomies in patients with chronic constipation, to prevent "autointoxication" from toxic bowel contents (1). This practice was eventually abandoned (along with the surgeon), but the concept of autointoxication has been revived, as the bowel is now recognized as a leading source of morbidity and mortality in critically ill patients.

This chapter describes abdominal infections that are related to the ICU stay, including infections of the gallbladder (acalculous cholecystitis), the bowel (*Clostridium diffcile* enterocolitis), and the peritoneal cavity (e.g., postoperative infections).

ACALCULOUS CHOLECYSTITIS

Acalculous cholecystitis (i.e., inflammation of the gallbladder without cystic duct obstruction by gallstones) is an uncommon form of acute cholecystitis that typically occurs in critically ill patients, and is more severe than its "calculous" counterpart (2,3).

Pathogenesis

Predisposing conditions include stroke, sepsis, circulatory shock, prolonged periods of bowel rest (i.e., during total parenteral nutrition), and the postoperative period (especially following cardiopulmonary bypass surgery) (3–6). Possible mechanisms include hypoperfusion, decreased gallbladder contractions (which allows the buildup of gallbladder "sludge"), relaxation of the sphincter of Oddi (which allows enteric pathogens to enter the biliary tree), and a change in the composition of bile. The latter mechanism is based on the observation that biliary sludge contains small crystals called "microliths" that can promote cholecystitis (7).

Clinical Features

The clinical presentation can be nonspecific, as fever, hypotension, and multiorgan failure are

common but nonspecific findings, while *pain and tenderness in the right upper quadrant can be absent in one-third of patients* (8). Blood cultures are positive in 90% of cases (8) and gram-negative aerobic bacilli are isolated in almost all cases.

Diagnosis

Ultrasound is favored as the initial diagnostic test for acalculous cholecystitis, but the diagnostic yield can be limited. Gallbladder distension and sludge are suggestive findings, but are nonspecific. Advanced disease may yield more specific findings, such as the ultrasound image in Figure 41.1, which shows sloughed mucosa in the lumen of the gallbladder that is characteristic of gangrenous cholecystitis.

The diagnostic yield from ultrasound varies widely in different reports; the pooled results from 26 studies show a sensitivity of 81% and a specificity of 83% (9). If ultrasound is not diagnostic, *the gold standard test for acalculous cholecystitis is the hepatobiliary iminodiacetic acid (HIDA) scan* (2), but this requires a functional liver to move the tracer into the bile ducts. Magnetic resonance imaging (MRI) has the same diagnostic yield as abdominal ultrasound, and the accuracy of computed tomography is poor (2).

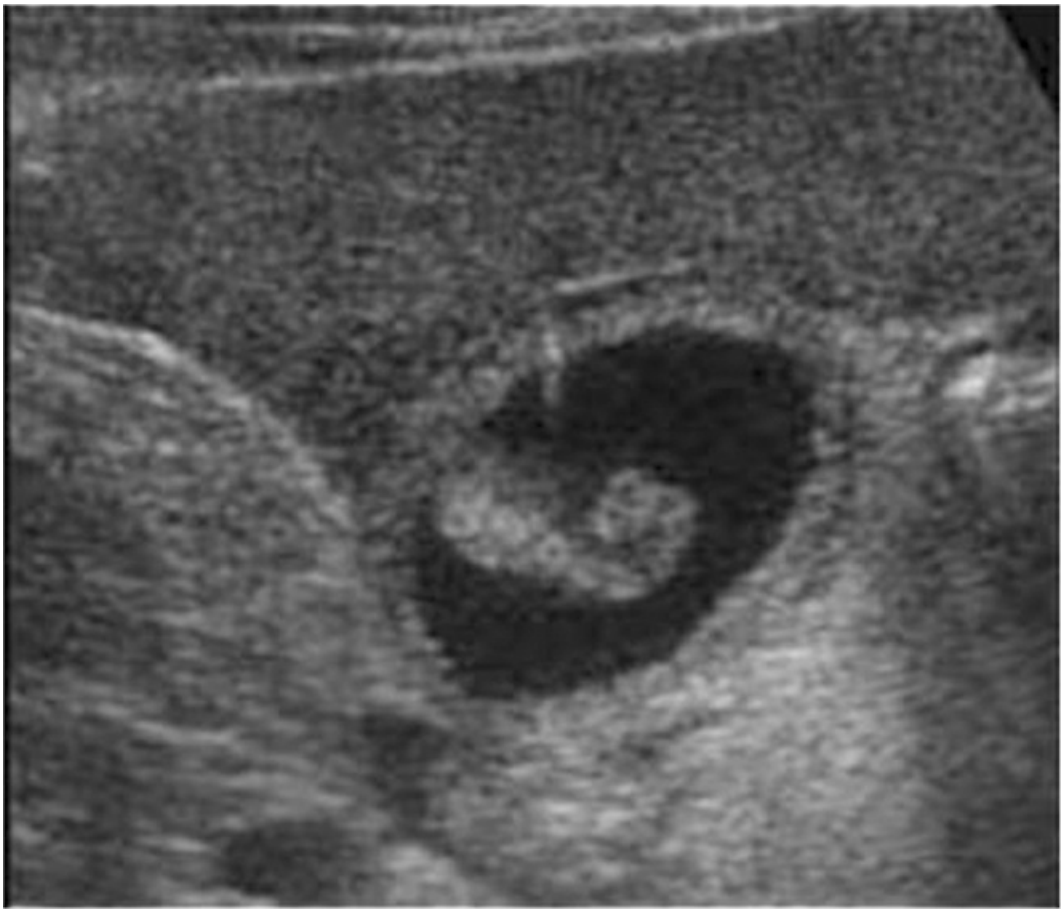

FIGURE 41.1 Transverse sonogram of the gallbladder showing marked thickening of the gallbladder wall and an echogenic mass projecting into the lumen of the gallbladder. This mass represents sloughed mucosa, and is characteristic of gangrenous cholecystitis.

TABLE 41.1 Antibiotic Penetration into Bile	
Good Penetration	**Poor Penetration**
Ampicillin/Sulbactam	Cefepime
Ceftriaxone	Cefotaxime
Ciprofloxacin	Ceftazidime
Levofloxacin	Gentamicin
Piperacillin/tazobactam	Meropenem
Tigecycline	Vancomycin

Management

Prompt intervention is mandatory, as this condition can deteriorate rapidly. Laparoscopic cholecystectomy is the treatment of choice (2), but for patients who are too unstable for surgery, percutaneous drainage of the gallbladder is a suitable alternative.

Empiric antibiotic therapy should be started as soon as the diagnosis is confirmed, and coverage should include gram-negative enteric organisms. Table 41.1 shows the penetration of different antibiotics into bile.

CLOSTRIDIUM DIFFICILE

As described in Chapter 4, the normal microbial environment in the GI tract, known as the *microbiome*, has an important role in preventing colonization by undesirable pathogens (10). Disruption of the microbiome, which is known as *dysbiosis*, can lead to a variety of infections (both localized and disseminated), and the most prominent of these infections is *Clostridium difficile* enterocolitis, which *is considered the most common healthcare-associated infection* (11). (*Note: Clostridium difficile* has been renamed *Clostridioides difficile*, but the original name will be used here.)

Pathogenesis

Clostridium difficile is a spore-forming gram-positive anaerobic bacillus that is an uncommon inhabitant of the bowel in healthy subjects, but is able to proliferate in the bowel when the normal microbial population has been altered. The major risk factors for *C. difficile* colonization are advanced age, contact with a healthcare facility, and antibiotic therapy (12,13). The organism is occasionally found in poultry, fish, and red meat (14), but the major route of transmission is the fecal-oral route.

C. difficile is not an invasive organism, but releases cytotoxins (Toxins A and B) that damage the bowel mucosa. This leads to inflammatory infiltration of the bowel wall and symptomatic disease. Severe inflammation is accompanied by raised, plaque-like lesions on the mucosal surface known as ‘pseudomembranes’. The presence of these lesions (*pseudomembranous colitis*) is evidence of severe disease.

The enterocolitis from *C. difficile* is primarily a nosocomial infection (i.e., appears after 48 hours of the hospital stay), and the organism is transmitted from patient-to-patient via the hands of hospital personnel. However, there has been a drastic rise in community-acquired *C. difficile* infections in recent years, and they now account for 34–48% of all cases (11).

Gastric Acid Suppression

There are several reports showing that use of acid-suppressing drugs, particularly proton pump inhibitors, is associated with an increased risk of *C. difficile* infection (15–17). This is consistent with the role of gastric acidity as an antibacterial defense mechanism, which is described in Chapter 4 (see Figure 4.3). The protective effect of gastric acid on *C. difficile* infections has important implications for the escalating and excessive use of gastric acid-suppressing drugs, particularly proton pump inhibitors, for stress ulcer prophylaxis in hospitalized patients. (This topic is revisited in the very last section of the chapter.)

Clinical Features

The principal manifestation of *Clostridium difficile* infection (CDI) is a watery diarrhea, which can be accompanied by a low-grade fever (≤101° F) and mild leukocytosis (WBC count <15,000/mm^3). Fulminant CDI occurs in 3–5% of cases (18), and is characterized by hypotension and abdominal distension from ileus, or from the most feared complication of CDI, toxic megacolon. The latter condition, which is shown in Figure 41.2, is a surgical emergency.

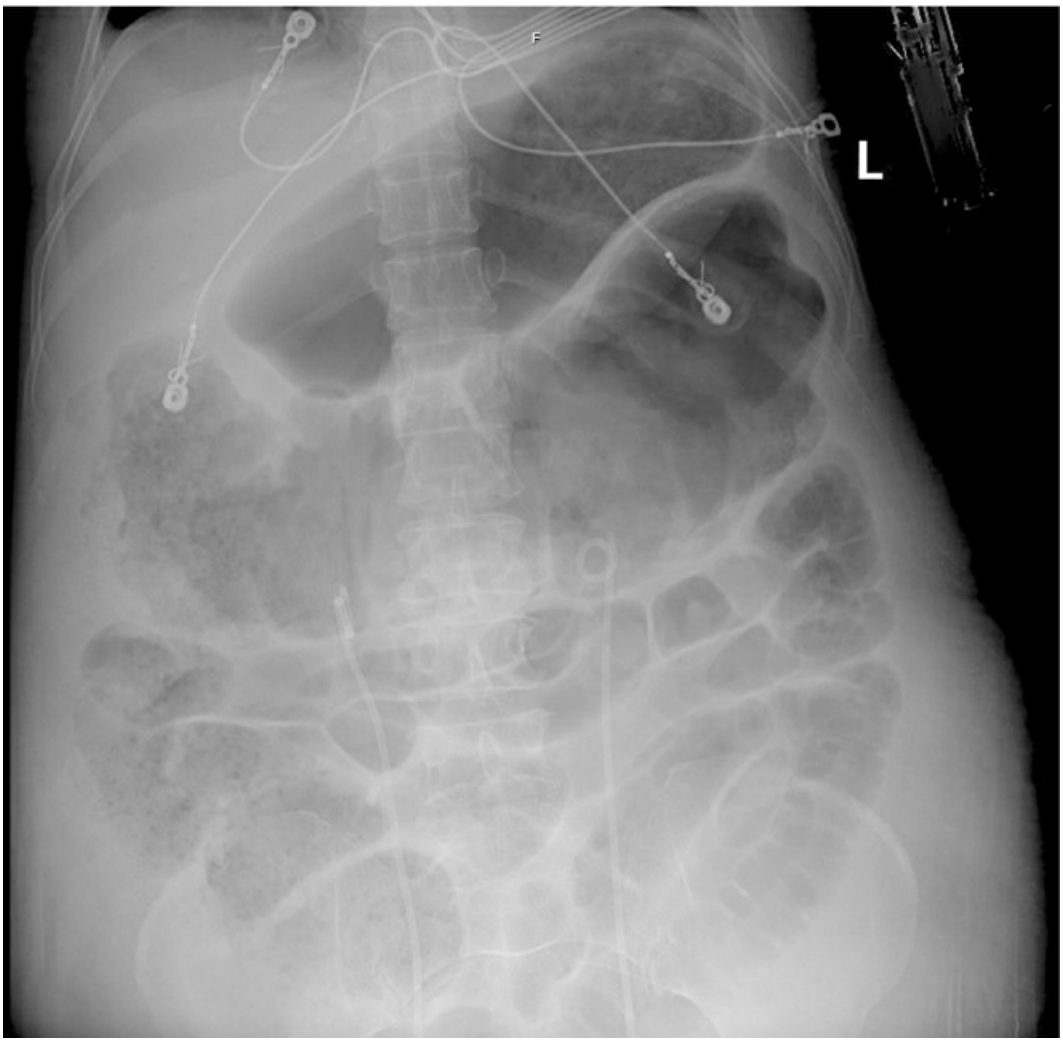

FIGURE 41.2 Radiographic appearance of toxic megacolon in a patient with *C. difficile* enterocolitis.

Diagnostic Evaluation

The following laboratory tests (on stool samples) are used for the diagnostic evaluation of CDI.

. A polymerase chain reaction (PCR) that detects the gene for Toxin B. A positive test confirms the presence of toxigenic *C. difficile*, but does not differentiate colonization from infection.

. An enzyme-linked immunosorbent assay (ELISA) that detects toxins A and B. A positive test confirms the diagnosis of CDI.

The flow diagram in Figure 41.3 shows how these tests are used in a case of suspected CDI. The PCR is highly sensitive, and is used as an initial screening test. A negative PCR eliminates the diagnosis of CDI (by eliminating the presence of toxigenic *C. difficile*). However, a positive PCR confirms colonization, but not infection, so an ELISA test for cytotoxins is warranted. A positive ELISA test confirms the diagnosis of CDI. However, the ELISA test has a low sensitivity, and can miss about 20% of cases of CDI (12), so a negative ELISA does not eliminate the possibility of CDI. Nevertheless, most patients who are PCR-positive but toxin-negative do well without treatment for CDI (19).

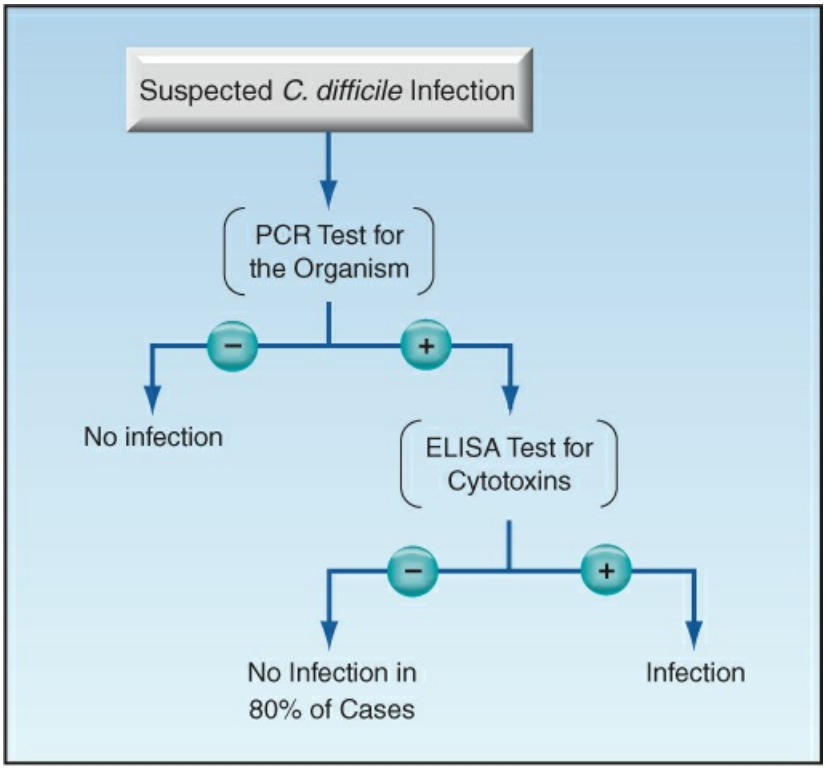

FIGURE 41.3 Flow diagram for the diagnostic evaluation of *C. difficile* infection. See text for explanation.

CAVEAT: There is a tendency to treat patients for CDI based on a positive PCR test only, but about half of patients who are PCR-positive do not have cytotoxins by immunoassay (19), and these patients do well without antibiotics (as just mentioned). Therefore, the treatment of CDI based on the PCR test alone should be discouraged, as it leads to the overdiagnosis of CDI, and the unnecessary use of antibiotics.

COLONOSCOPY: Direct visualization of the bowel mucosa is reserved for the occasional case where there is a high clinical suspicion of CDI that is not confirmed by the cytotoxin assay. The presence of pseudomembranes confirms the diagnosis of CDI. Colonoscopy is preferred to proctosigmoidoscopy for optimal results.

Treatment

The recommended antibiotic regimens for CDI are shown in Table 41.2 (13), and are summarized below.

. The treatment of choice for routine cases of CDI is oral vancomycin or fidaxomicin in the doses shown in Table 41.2. The fever resolves in 24 to 48 hrs, and the diarrhea resolves in 4 to 5 days (20), but treatment is continued for 10 days.

. Fulminant cases of CDI should be treated with a combination of enteral vancomycin and IV metronidazole. If surgery is needed for toxic megacolon, subtotal colectomy is preferred (13).

. Relapses (usually within 3 weeks) are reported in 25% of cases treated with vancomycin (21), and 13% of cases treated with fidaxomicin (22). If vancomycin was used initially, the first recurrence is treated with a 10-day course of fidaxomycin or an extended course of vancomycin, as shown in Table 41.2.

TABLE 41.2 Antibiotic Therapy for *Clostridium difficile* Infection (CDI)

Condition	Recommendations
Initial Episode	Vancomycin: 125 mg PO four times daily for 10 days, *OR* Fidaxomicin: 200 mg PO twice daily for 10 days.
Fulminant CDI	Vancomycin: 500 mg every 6hrs by mouth, NG tube, or rectal enema, *PLUS* Metronidazole: 500 mg IV every 8 hrs.
1st Recurrence	Vancomycin: 125 mg PO four times daily for 10–14 days, then twice daily for 7 days, then daily for 7 days, then every 2–3 days for 2–8 wks, *OR* Fidaxomicin: 200 mg PO twice daily for 10 days. (Only if vancomycin was used for the initial R_x).
2nd Recurrence	Fecal microbiota transplantation

From the clinical practice guidelines in Reference 13.

Fecal Transplantation

About 5% of patients with CDI have more than one relapse (20), and the most effective treatment for multiple relapses is “fecal microbiota transplantation”, which is a fancy term for the instillation of liquid stool from healthy donors (via nasogastric tube, endoscopy, or enemas) to re-establish a normal microbial environment in the GI tract. The reported cure rate is a remarkable 80–100% for recurrent CDI (23).

Preventive Measures

Prophylactic measures are aimed at preventing transmission of the organism from patient to

patient, and preventing colonization of the organism in susceptible patients.

Infection Control

The guidelines from the Infectious Diseases Society of America recommends gloves and gowns for any contact with an infected patient, and handwashing before and after each patient contact (13). However, these measures are unlikely to eliminate spread of this disease, because asymptomatic carriers of *C. difficile* are important sources of transmitted disease (13).

Probiotics

Probiotics (i.e., non-pathogenic organisms that bind to epithelial cells and prevent the attachment of *C. difficile*) are widely used during and after treatment of CDI (24), but this is not recommended by the American College of Gastroenterology (12) because of inconclusive study results, and evidence that *probiotics can actually impede recolonization of the colon following antibiotic therapy* (25).

COMPLICATED INTRA-ABDOMINAL INFECTIONS

Complicated intra-abdominal infections are defined as infections that involve the peritoneal cavity, and can be a generalized peritonitis or a localized abscess (26). They are often the result of a rupture or tear somewhere along the gastrointestinal tract, or an anastomotic leak following abdominal surgery. These infections can be difficult to treat, and they require prompt source control (i.e., closure of the bowel perforation) and appropriate empiric antibiotics.

Bowel Perforation

Perforations of the GI tract can arise from a wide variety of conditions, including trauma, peptic ulcer disease, bowel ischemia or obstruction, inflammatory or neoplastic disease, rupture of diverticuli, or unintentional laceration of the bowel during surgery. Abdominal pain is almost universal, and there may be signs of peritoneal irritation (guarding and rebound tenderness). Progression to circulatory shock can be rapid (26).

Diagnosis

The diagnosis of bowel perforation requires evidence of free air in the peritoneal cavity (pneumoperitoneum). The presence of free air under the diaphragm in an upright chest x-ray, as shown in Figure 41.4, has a reported sensitivity of up to 85% for the detection of bowel perforations (27). CT scans are more sensitive than plain radiographs, and they can localize the site of the perforation in 85% of cases (28). Pneumoperitoneum is not a useful finding shortly after abdominal surgery, as it can persist for at least one week after the procedure (29).

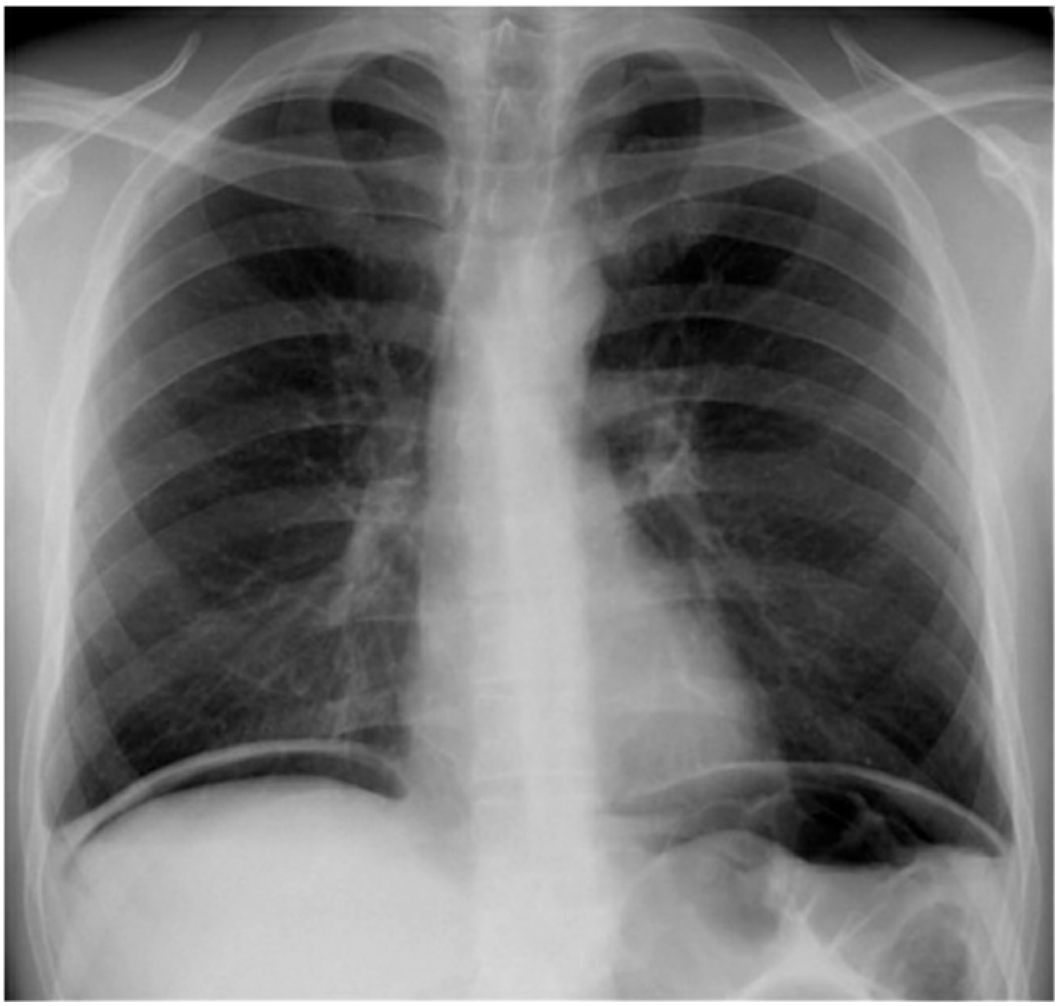

FIGURE 41.4 A chest x-ray in the upright position showing free air under both hemidiaphragms.

Management

Immediate surgical exploration is typically the first priority for bowel perforations, but the perioperative management should include the following measures.

FLUIDS: Soiling with bowel contents can be accompanied by considerable fluid loss into the peritoneal cavity, so signs of circulatory compromise (i.e., a decrease in urine output or blood pressure) should prompt appropriate volume resuscitation. Avoiding vasopressor therapy is optimal prior to surgery (if possible), because it promotes splanchnic vasoconstriction, which will aggravate an underlying ischemic condition in the bowel.

TABLE 41.3 Antibiotic Coverage for Enteric Organisms

	Gm⁻ Aerobic Bacilli	*Pseudomonas* Species	Enterococci (non-resistant)	Anaerobic Organisms	ESBLs
Piperacillin/ tazobactam	+	+	+	+	+ / –
Meropenem	+	+	+ / –	+	+
Tigecycline	+	–	+	+	+
Ceftazidime/ avibactam	+	+	–	–	+
Amikacin	+	+	–	–	+ / –
Ceftriaxone	+	–	–	–	–
Metronidazole	–	–	–	+	–

ESBLs = extended-spectrum beta-lactamases.

ANTIBIOTICS: Empiric antibiotic therapy should be started as soon as possible using antibiotics that are active against enteric pathogens. The coverage of selected antibiotics is shown in Table 41.3. This is used to make the following recommendations, which are taken from recently published guidelines on intra-abdominal infections (26):

. If no resistant organisms are suspected, *piperacillin-tazobactam* is suitable for single-agent empiric coverage (26). The combination of *ceftriaxone* and *metronidazole* is an alternative recommendation for patients that are not seriously ill, but the coverage is far inferior to piperacillin-tazobactam.

. Organisms that produce extended-spectrum beta-lactamases (ESBLs) are resistant to penicillins and third-generation cephalosporins. If these organisms are suspected (e.g., from prior colonization or infection), the antibiotic options are *meropenem*, *tigecycline*, and *ceftazidime/avibactam*.

a. Meropenem provides the broadest coverage, and is the treatment of choice in patients with septic shock (26). However, there is a reason to limit its use because of rapidly developing resistance (30). Of note, meropenem is not active against methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococci (VRE).
b. Tigecycline does not cover *Pseudomonas* species, but it is active against MRSA and VRE. It is not recommended in patients with septic shock (26).
c. Ceftazidime/avibactam is one of the newer group of beta-lactam antibiotics that contains a beta-lactamase inhibitor (avibactam). Ceftazidime provides coverage for *Pseudomonas*

species, but it is not active against enterococci or anaerobic organisms. The experience with this antibiotic combination is limited at present.

. For patients that are allergic to beta-lactam antibiotics, the combination of amikacin and metronidazole provides suitable coverage.

CANDIDA COVERAGE: *Candida albicans* and related species can be prominent inhabitants of the bowel (especially in patients who have received antibiotics recently), and *perforation in the upper GI tract has been identified as a major risk factor for Candida peritonitis* (31). If this is a concern, empiric coverage should include an antifungal agent that covers all *Candida* species, such as one of the echinocandins (i.e., *micafungin, anidulafungin,* or *caspofungin*).

Postoperative Infections

Postoperative peritonitis is the most common abdominal infection in ICU patients (32), and is usually the result of anastomotic leakage. The management is similar to that described for bowel perforations, with the following exceptions (32):

. The empiric antibiotic regimen should include coverage for ESBL-producing organisms.

. Empiric coverage for *Candida* species is recommended in unstable or critically ill patients.

These infections are problematic because there is often a delay in recognizing an anastomotic leak, which is partly due to the presence of peritoneal air for at least one week after abdominal surgery. Return to the operating room is often prompted by a deterioration in the patient's clinical condition, which increases the risk associated with the reoperation. There is some evidence that C-reactive protein levels can be used to predict the likelihood of an anastomotic leak (33), but this has not gained widespread acceptance.

Abscess

Postoperative abdominal abscesses are often an occult source of sepsis, and are difficult to uncover with routine clinical evaluations. Fever is almost always present, but localized abdominal tenderness can be absent in 60% of cases, and a palpable abdominal mass is evident in less than 10% of cases (34,35). Abdominal x-rays can show extraluminal air, but this occurs in less than 15% of cases (35).

DIAGNOSIS: Computed tomography (CT) of the abdomen is the most reliable method of detecting abdominal abscesses. However, CT imaging in the early postoperative period can be misleading because collections of blood or irrigant solutions in the peritoneal cavity can be misread as an abscess. CT scans are most reliable when performed after the first postoperative week (when peritoneal fluid collections have resorbed) (35). The CT appearance of an abdominal abscess is shown in Figure 41.5.

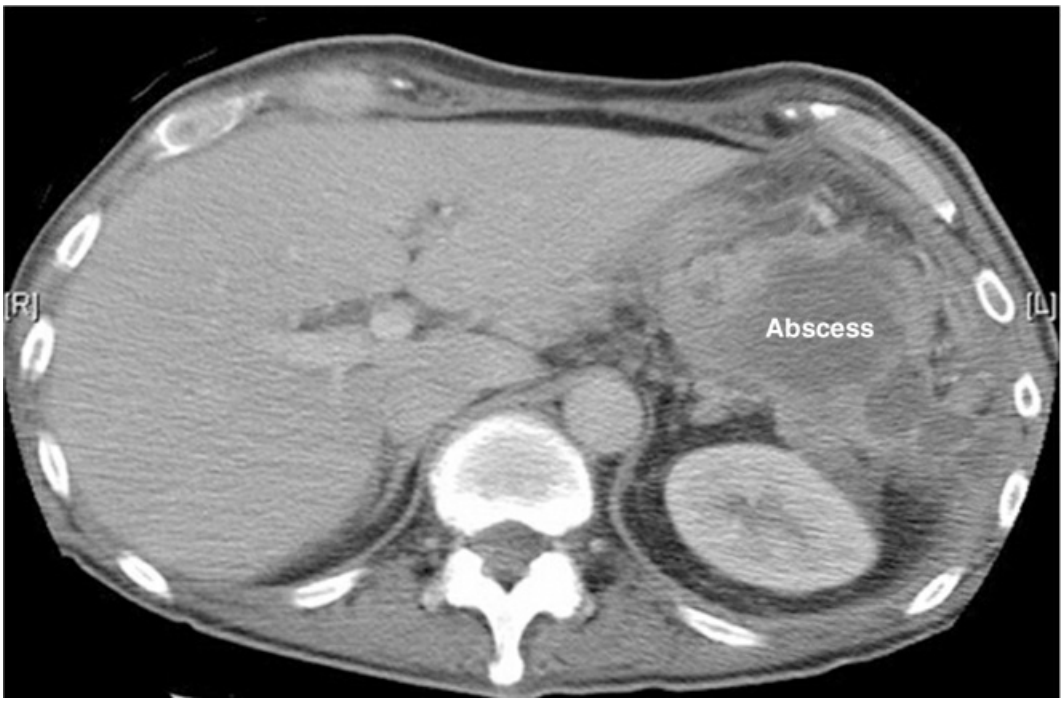

FIGURE 41.5 Abdominal CT scan showing a multiloculated abscess in the left upper quadrant in a post-splenectomy patient.

MANAGEMENT: Immediate drainage is advised for postoperative abdominal abscesses. CT-guided drainage is successful in 90–95% of cases (36), and surgery is rarely needed. The empiric antibiotic regimen is the same as described for postoperative peritonitis.

A FINAL WORD

C. difficile and Gastric Acid

The role of gastric acid as an antibacterial defense against ingested microbes (which is described in Chapter 4) does not receive the attention it deserves. One example of this is the evidence that suppression of gastric acidity with proton pump inhibitors promotes the transmission of *Clostridium difficile* infections (15–17), which has hardly curbed the excessive use of proton pump inhibitors for stress ulcer prophylaxis.
The following observation deserves mention:

> There was a marked increase in the incidence of *C. difficile* infections in the first decade of the 21st century, at the same time that proton pump inhibitors gained widespread use for stress ulcer prophylaxis (37).

Is this serendipity, or a causal link? Whatever the answer, the antibacterial actions of gastric acidity are reason enough to curb the excessive use of gastric-acid suppressing drugs for stress ulcer prophylaxis.

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Chapter 42

Urinary Tract Infections in the ICU

Throughout nature, infection without disease is the rule rather than the exception.

René Dubos (*a*)

Indwelling bladder catheters are commonplace in critically ill patients, and catheter-associated urinary tract infections are cited as the most prevalent nosocomial infections in the United States (1). However, this claim may be misleading, since there is a tendency to confuse asymptomatic bacteriuria (i.e., *infection without disease*) with catheter-associated infections. This chapter describes the relevant features of catheter-associated urinary tract infections (UTIs), including pathogenesis, prevention, diagnostic criteria, and treatment.

PATHOGENESIS

The presence of an indwelling bladder catheter is associated with a 3–8% incidence of bacteriuria ($\geq 10^5$ colony forming units/mL) *per day* (2). Bacteria (mostly of bowel origin) form *biofilms* on the inner and outer surface of urethral catheters (3), and these biofilms can serve as a source of continued microbial colonization in the bladder. However, this is not the full story, because *direct injection of pathogens into the bladder of healthy subjects does not result in an infection* (4).

Bacterial Adherence

The missing piece of the puzzle is the ability of pathogenic organisms to adhere to the bladder epithelium. The epithelial cells of the bladder are normally coated with commensal (non-pathogenic) organisms, as shown in Figure 42.1 (5), and this prevents the attachment of pathogenic organisms, which serves as a prelude to urinary tract infections (2,3). This is the same phenomenon that occurs in colonization of the oral mucosa with pathogenic microbes (see Figure 5.5), which is a prelude to nosocomial pneumonia. The presence of a bladder catheter triggers a localized inflammatory response in the bladder epithelium, with exfoliation of the normal epithelial lining, and this is believed to favor the attachment of urinary pathogens (3).

Microbiology

A multistate survey of the organisms isolated in catheter-associated UTIs (6) included (in order of decreasing prevalence) *Escherichia coli* (28% of cases), *Klebsiella pneumoniae* (23%), enterococci (17%), *Pseudomonas aeruginosa* (10%), *Candida* species (5%), staphylococci (3%) and streptococci (3%). A single organism predominates in short-term catheterization (<30 days), while polymicrobial infections are common in long-term catheterization (≥30 days) (7).

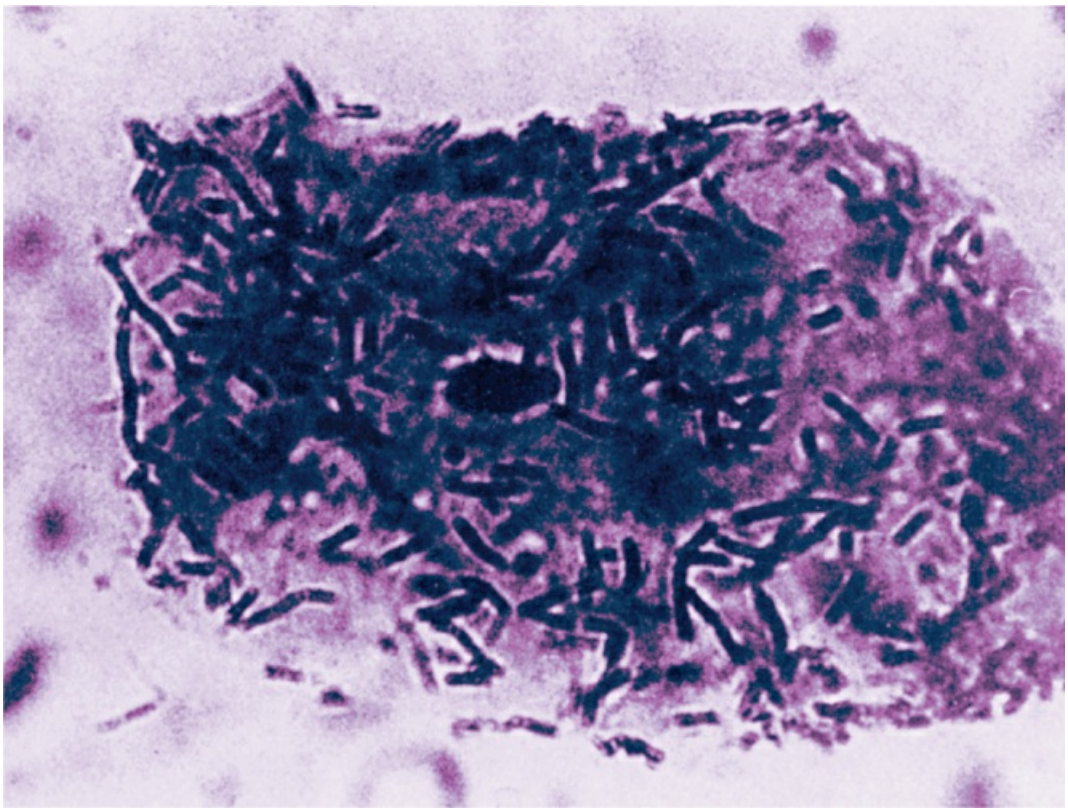

FIGURE 42.1 Photomicrograph showing non-pathogenic *Lactobacillus acidophilus* organisms adhering to a bladder epithelial cell. Image from Reference 5, digitally enhanced.

Prevention

The risk of catheter-associated infection is determined primarily by the duration of catheterization. This is demonstrated in the graphs in Figure 42.2, which show that early removal of urethral catheters reduces the risk of both asymptomatic bacteriuria and catheter-associated infections (8). Removing catheters when they are no longer necessary is the single most effective measure for preventing catheter-associated infections. Other observations about prevention are summarized below.

. Daily cleansing of catheter insertion sites (with antiseptic solutions, antibiotic creams, or soap and water) is not recommended, because this practice can increase the risk of bacteriuria (2).

. Prophylaxis with systemic antibiotics is not recommended (2).

. Antimicrobial-impregnated urinary catheters (i.e., with silver alloy) can reduce the incidence of catheter-associated infections, but only if combined with regular replacement of catheters (9).

DIAGNOSIS AND TREATMENT

The diagnosis of catheter-associated UTIs (CAUTIs) is based on criteria presented by the National Healthcare Safety Network (NHSN) (10), which is a division of the Centers for Disease Control (CDC) that monitors healthcare-associated infections in the United States.

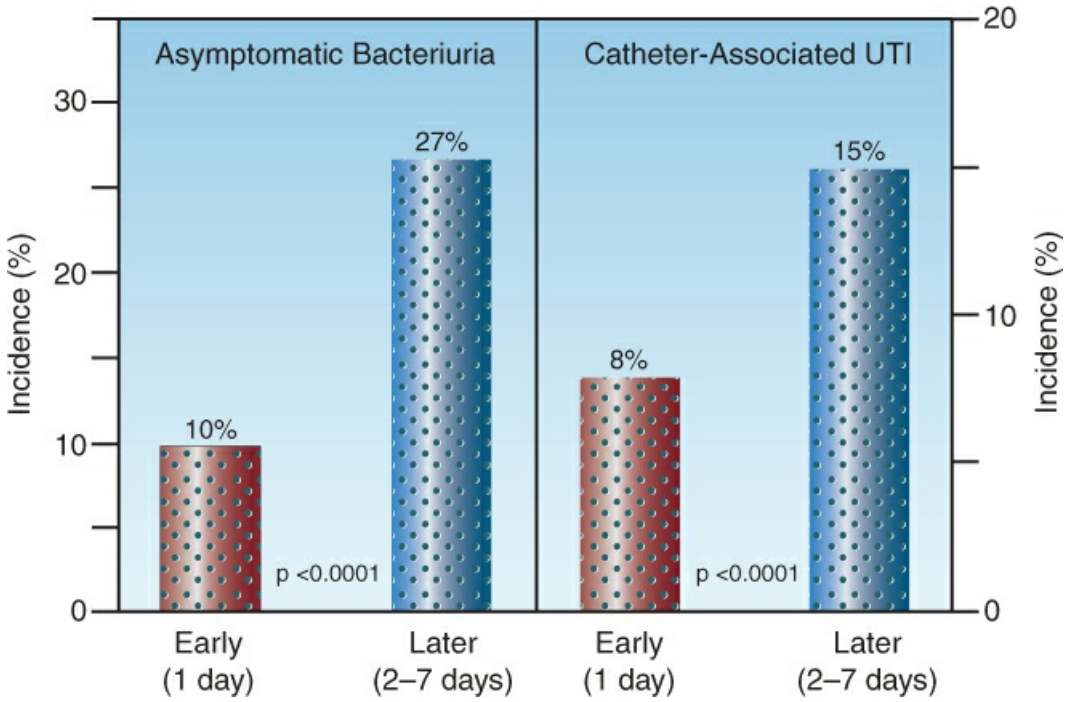

FIGURE 42.2 Graphs showing that the early removal of urethral catheters significantly reduces the incidence of both asymptomatic bacteriuria and catheter-associated infection. Data represents the pooled results of 16 clinical trials, from Reference 8.

Diagnostic Criteria

The diagnosis of CAUTI requires all of the following:

. The presence of an indwelling urethral catheter for at least two consecutive days in an inpatient setting, and the catheter is either still in place, or it has been removed the day before the suspected infection.

. The patient should experience at least one of the following:

a. Fever (>38° C or 100.4° F)
b. Suprapubic tenderness
c. Costovertebral pain or tenderness
d. Urinary urgency or frequency
e. Dysuria

Note: The last two criteria do not apply to patients with indwelling catheters.

. The urine culture should identify no more than two species of organisms, and at least one species should be a bacterium with a growth of $>10^5$ colony-forming units per mL (cfu/mL).

Fever

The inclusion of fever as a diagnostic criterion for CAUTI is problematic, because there are a multitude of potential causes of fever in ICU patients (see Chapter 44). The nonspecific aspect of fever is demonstrated by a comparison study of patients with and without CAUTI, where the incidence of fever was the same in both groups of patients (11).

Pyuria

Pyuria (i.e., >10 white blood cells per high-powered field in centrifuged urine) is not diagnostic of CAUTI, since there are noninfectious inflammatory conditions that can cause pyuria. However, *the absence of pyuria is evidence against the diagnosis of CAUTI* (2).

Bacteremia

About 20% of bacteremias in hospitalized patients are the result of CAUTI (8), but bacteremia is not included as a diagnostic criterion for CAUTI. However, the NHSN has a diagnostic entity called *Asymptomatic Bacteremic Urinary Tract Infection* (ABUTI), which is a patient with or without a urethral catheter that is asymptomatic but has significant bacteriuria ($>10^5$ cfu/mL) with an organism that is also growing in blood cultures. In other words, *if the same bacterium is isolated in blood and urine cultures (and growth in the urine culture is $>10^5$ cfu/mL) the diagnosis is a UTI, regardless of the presence or absence of symptoms*. This does not apply to *Candida* species, as described later.

Asymptomatic Bacteriuria

The diagnosis of asymptomatic bacteriuria thus requires the following:

. A urine culture that shows growth of a single bacterium with a colony count $>10^5$ cfu/mL.

. Blood cultures that show no growth of the bacterium identified in the urine culture.

. The absence of symptoms related to a UTI.

Treatment

. Antibiotic treatment of patients with asymptomatic bacteriuria is not advised unless the patient is scheduled for a urologic procedure that results in mucosal bleeding (12).

. Empiric antibiotics are recommended for patients with suspected CAUTI, and should provide coverage for gram-negative aerobic bacilli and enterococci.

a. Single agent therapy with *piperacillin-tazobactam* or a carbapenem (e.g., *meropenem*) is suitable (13).

b. Alternative (second-line) agents include *ceftazidime*, *cefepime*, or a fluoroquinolone (e.g., *levofloxacin*) (13).

. If the diagnosis of CAUTI is confirmed by urine culture, antibiotic therapy should be tailored to the isolated organism and microbial sensitivities. Catheters that have been in place for longer than two weeks should be replaced or removed if no longer necessary (2).

. The duration of antibiotic therapy for CAUTI should be 7 days for patients who respond promptly, and 10–14 days otherwise (2,13).

Candiduria

The presence of *Candida* species in urine usually represents colonization in patients with indwelling urethral catheters, but candiduria can also be a sign of disseminated candidiasis (i.e., the candiduria being the result, not the cause, of the disseminated candidiasis). In fact, *candiduria may be the only evidence of disseminated disease*, since blood cultures are unrevealing in more than 50% of cases of disseminated candidiasis (14).

Microbiology

In cases of candiduria, the colony count has no predictive value for identifying renal or disseminated candidiasis (14). The most frequent isolate is *C. albicans* (about 50% of cases), followed by *C. glabrata* (14,15). The latter organism is notable for resistance to the antifungal agent fluconazole.

Asymptomatic Candiduria

Asymptomatic candiduria does not require treatment unless the patient is neutropenic (and is at risk for disseminated candidiasis) (15,16); in this case, the recommended prophylaxis is an echinocandin (i.e., *caspofungin, micafungin,* or *anidulafungin*) (16).

Symptomatic Candiduria

Candiduria that is associated with fever, suprapubic tenderness, or costovertebral tenderness requires antifungal therapy as well as blood cultures and imaging studies of the kidneys (with ultrasound or computed tomography) to search for renal abscesses or evidence of urinary tract obstruction.

. If systemic candidiasis is suspected, or is verified by positive blood cultures, the recommended treatment is an echinocandin. These agents are preferred to fluconazole because they are active against all *Candida* species.

. The recommended treatment for *Candida* UTIs (cystitis or pyelonephritis) is dependent on the organism (16).

a. For *Candida* species that are sensitive to fluconazole (e.g., *Candida albicans*), the treatment is *oral fluconazole* (200–400 mg daily for 2 weeks) (17).

b. For fluconazole-resistant organisms (i.e., *Candida glabrata* and *Candida krusei*), the recommended treatment is *amphotericin B* (0.3–0.6 mg/kg daily for 1–7 days). The echinocandins are not recommended in this situation because of poor penetration into the urine.

. For *Candida* UTIs associated with fungus balls, surgical intervention is recommended. If nephrostomy tubes are present, irrigation with *amphotericin B* (25–50 mg in 200–500 mL sterile water) is recommended.

A FINAL WORD

Bacterial Adherence & Nosocomial Infections

The unifying feature in nosocomial infections that involve the gastrointestinal, respiratory, and urinary tracts is a change in the character of microbes that adhere to epithelial surfaces. In healthy subjects, the epithelial surfaces in the mouth, GI tract, and urinary tract are colonized by harmless microbes, but this changes in patients who are seriously ill, when the epithelial surfaces become populated with pathogenic organisms. This pathogenic colonization then serves as a prelude to nosocomial infections.

The colonization of epithelial surfaces is not a function of microbial density (where the most densely populated organisms take up the space on the epithelial surface), but rather is determined by the ability of bacteria to bind to the epithelial cells. For example, pathogenic *E. coli* (the most common cause of CAUTIs) have specialized appendages called *pili* that can bind to glycoproteins on bladder epithelial cells, and there are small carbohydrate molecules (such as mannose) that can competitively block this binding (3). Observations like this suggest a novel approach to the prevention of nosocomial infections by preventing the adhesion of pathogenic organisms to epithelial surfaces. This approach is appealing because it does not require prophylactic antibiotics, and thus would limit the emergence of resistant organisms.

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Section XIII

ALTERED BODY TEMPERATURE

There is no possibility of escaping the entropic doom imposed on all natural phenomena.

Aharon Katchalsky
1965

Chapter 43

Thermoregulatory Disorders

Heat not a furnace for your foe so hot that you singe yourself.

Shakespeare
Henry VIII

The human body is a metabolic furnace that generates enough heat to raise the body temperature by 1° C every hour, even at rest (1). Fortunately, the external surface of the body acts like a radiator, and discharges excess heat into the surrounding environment. The behavior of this radiator is guided by a thermostat (the thermoregulatory system) that limits the daily variation in body temperature to ±0.6° C (2). This chapter describes what happens when this thermostat fails, and allows the body temperature to rise or fall to life-threatening levels.

HEAT-RELATED ILLNESS

Hyperthermia vs. Fever

The distinction between *hyperthermia* and *fever* deserves mention at the outset. Both conditions are characterized by an elevated body temperature, but hyperthermia is the result of a defect in temperature regulation, while fever is the result of a normal thermoregulatory system operating at a higher set point. The elevations in body temperature in this chapter represent hyperthermia, not fever. Because the underlying mechanisms involved in the production of hyperthermia and fever are different, *the antipyretic agents used to treat fever (e.g., acetaminophen) are ineffective in hyperthermia*.

Response to Thermal Stress

The maintenance of body temperature in conditions of thermal stress (e.g., hot weather, strenuous exercise) is primarily achieved by enhanced blood flow to the skin (convective heat loss) and the loss of sweat (evaporative heat loss).

Convective Heat Loss

When heat is lost from the skin, it warms the air just above the skin surface, and the increase in

surface temperature limits the further loss of body heat by conduction. However, when an air current (e.g., from a fan or gust of wind) is passed across the skin, it displaces the warm layer of air above the skin and replaces it with cooler air, and this process facilitates the continued loss of body heat by conduction. The same effect is produced by increases in blood flow just underneath the skin. The action of currents (air and blood) that promote heat loss is known as *convection*.

Evaporative Heat Loss

The transformation of water from a liquid to a gas requires heat (called the 'latent heat of vaporization'), and the heat required for the evaporation of sweat from the skin is provided by body heat. The evaporation of one liter of sweat from the skin is accompanied by the loss of 580 kilocalories (kcal) of heat from the body (3). This is about one-quarter of the daily heat production by an average-sized adult at rest. Thermal sweating (as opposed to "nervous sweating") can achieve rates of 1 to 2 liters per hour (3), which means that over 1,000 kcal of heat can be lost in one hour during profuse sweating. It is important to emphasize that *sweat must evaporate to ensure loss of body heat. Wiping sweat off the skin will not result in heat loss*, so this practice should be discouraged during strenuous exercise.

Syndromes

Heat-related illnesses are conditions where the thermoregulatory system is no longer able to maintain a constant body temperature in response to thermal stress. There are a number of minor heat-related conditions, such as *heat edema* (dependent soft tissue swelling), *heat cramps* (exercised-induced muscle cramps), and *heat rash* (a papular rash caused by blocked sweat pores) (4), but the following descriptions are limited to the major heat-related illnesses: *heat exhaustion* and *heat stroke*. The comparative features of these conditions are shown in Table 43.1 (3–5).

TABLE 43.1 Comparative Features of Heat Exhaustion and Heat Stroke

Feature	Heat Exhaustion	Heat Stroke
Body Temperature	38–39° C or 100.4–102° F	≥41° C or ≥106° F
CNS Dysfunction	No	Yes
Sweat Production	Yes	No
Dehydration	Yes	Yes
Hemodynamic Instability	No	Yes
Multiorgan Involvement	No	Yes

Heat Exhaustion

Patients with heat exhaustion experience flu-like symptoms that include hyperthermia (usually <38–39° C or 100.4–102° F), muscle cramps, nausea and malaise. The hallmark of this condition is *dehydration without signs of hemodynamic compromise*. The volume loss can be accompanied by hypernatremia (from sweat loss) or hyponatremia (when sweat loss is replaced with water

intake). Mentation is usually intact.

The management of heat exhaustion includes volume repletion and other general supportive measures (e.g., placing the subject in an air conditioned room). Active cooling measures are not necessary.

Heat Stroke

Heat stroke is a life-threatening condition characterized by extreme elevations in body temperature (≥41° C [≥106° F]), severe neurologic dysfunction (e.g., delirium, coma, and seizures), severe volume depletion with hypotension, and multiorgan involvement that includes rhabdomyolysis, acute kidney injury, disseminated intravascular coagulopathy (DIC), and marked elevation in serum transaminases, presumably from "ischemic hepatitis". The inability to produce sweat (anhidrosis) is a typical, but not universal, feature of heat stroke (5).

There are two types of heat stroke: (*a*) *classic heat stroke*, which is related to environmental temperatures, and (*b*) *exertional heat stroke*, which is related to strenuous exercise. Exertional heat stroke tends to be more severe, with a higher incidence of multiorgan dysfunction.

Management

The management of heat stroke includes volume resuscitation and active cooling measures to reduce the body temperature to 38° C (100.4° F).

EXTERNAL COOLING: External cooling in the field is best achieved by immersion in cold water or ice water. If these are not available, *evaporative cooling* is effective. This involves spraying the skin with cool water and then fanning the skin to promote evaporation. This method can reduce the body temperature at a rate of 0.3° C (0.6° F) per minute (6). Evaporative cooling is most effective when the weather is hot and dry (which enhances evaporation from the skin).

External cooling in the emergency department is accomplished by placing ice packs in the groin and axilla, and covering the upper thorax and neck with ice (7). Cooling blankets are then placed over the entire length of the body.

The major drawback of external cooling is the risk of shivering, which is counter-productive because it raises the body temperature.

INTERNAL COOLING: Internal cooling can be achieved with intravenous infusion of cold saline (4° C). Faster cooling has been reported with automated intravascular cooling devices (8) (i.e., the ones used for targeted temperature management in comatose survivors of cardiac arrest), but this approach requires central venous access, and the impact on outcomes has not been adequately studied.

Rhabdomyolysis

Skeletal muscle injury (rhabdomyolysis) is a common complication of hyperthermia syndromes, including heat stroke and the drug-induced hyperthermia syndromes (described later in the chapter). Disruption of myocytes in skeletal muscle leads to the release of creatine kinase (CK) into the bloodstream, and the measurement of CK levels in plasma is used to determine the presence and severity of rhabdomyolysis. There is no standard plasma CK level for the diagnosis of rhabdomyolysis, but levels that are at least five times normal have been suggested (9).

The adverse consequence of rhabdomyolysis are muscle weakness and acute kidney injury. The latter condition is the result of renal tubular injury from the myoglobin released by disrupted myocytes (10). The acute kidney injury from rhabdomyolysis is described in Chapter 34, along with the management of rhabdomyolysis.

DRUG-INDUCED HYPERTHERMIA SYNDROMES

Hyperthermia can also be a drug-related disorder, and three drug-related hyperthermia syndromes are recognized:

. Malignant Hyperthermia

. Neuroleptic Malignant Syndrome

. Serotonin Syndrome

Each of these is briefly described in this section.

Malignant Hyperthermia

The relevant features of malignant hyperthermia (MH) are summarized in Table 43.2. This condition is a rare inherited disorder with an autosomal dominant pattern that affects about 1 in 50,000 adults (11). It is characterized by excessive release of calcium from the sarcoplasmic reticulum in skeletal muscle in response to halogenated inhalational anesthetic agents (e.g., halothane, isoflurane) and depolarizing neuromuscular blockers (e.g., succinylcholine) (11).

TABLE 43.2 Malignant Hyperthermia

Predisposing Conditions:

A susceptible patient who has received:

1. A halogenated volatile anesthetic agent (e.g., halothane) or
2. A depolarizing neuromuscular blocker (e.g., succinylcholine)

Clinical Presentation:

1. Muscle rigidity
2. Increase in temp to ≥40° C
3. Altered mentation
4. Autonomic instability

Management:†

1. Dantrolene:
   a. 1–2 mg/kg as a rapid IV bolus, and repeat every few minutes until symptoms resolve or the cumulative dose reaches 10 mg/kg.
   b. Follow with oral or IV doses of 1–2 mg/kg every 6 hours for at least 24 hrs (to prevent recurrence).
2. Aggressive fluid infusion may be necessary for autonomic instability or rhabdomyolysis.

†Advice for acute management is available on the Malignant Hyperthermia Hotline: 1-800-644-9737. Dantrolene dosing regimen from Reference 13.

Clinical Manifestations

The first sign of MH may be a sudden and unexpected rise in end-tidal PCO_2 (11,12), which is a reflection of the increased metabolic rate caused by calcium-induced uncoupling of oxidative phosphorylation. This is followed (within minutes to a few hours) by muscle rigidity, which can begin in the masseter muscle before it becomes generalized. The heat generated by the combination of the hypermetabolism and muscle rigidity results in a marked rise in body temperature (often >40° C or 104° F), which generally occurs later in the presentation (12).

Neurologic dysfunction is commonplace in MH, with altered mentation (e.g., confusion, delirium, coma) and autonomic instability (e.g., fluctuating blood pressure, tachycardia). Rhabdomyolysis is also common, and can be accompanied by acute kidney injury from myoglobinuria.

Management

The first suspicion of MH should prompt immediate discontinuation of the offending anesthetic agent.

DANTROLENE: Specific treatment for the muscle rigidity is available with *dantrolene* sodium, a muscle relaxant that blocks the release of calcium from the sarcoplasmic reticulum. When given early in the course of MH, dantrolene can reduce the mortality rate from ≥70% (in untreated cases) to ≤10% (11,12). The dosing regimen for dantrolene is shown in Table 43.2 (13).

The most common side effect of dantrolene is muscle weakness, particularly grip strength, which usually resolves in 2 to 4 days after the drug is discontinued (13). The most troublesome side effect is hepatocellular injury, which is a risk with oral dantrolene, but requires months of treatment (13).

OTHER CONCERNS: Aggressive fluid infusion may be necessary for autonomic instability or rhabdomyolysis. If rhabdomyolysis develops, vigilance for hyperkalemia and acute kidney injury is necessary. Control of the rigidity should reduce the body temperature, and active cooling measures are usually not necessary.

Note: There is a Malignant Hyperthermia Hotline (1-800-644-9737) that provides advice for the acute management of MH.

Followup

All patients who survive an episode of MH should be given a medical bracelet that identifies their susceptibility to MH. In addition, because MH is a genetic disorder with an autosomal dominant inheritance pattern, immediate family members should be informed of their possible susceptibility to MH. (For testing options, see the website for the Malignant Hyperthermia Association of the United States – mhaus.org.)

Neuroleptic Malignant Syndrome

The neuroleptic malignant syndrome (NMS) is similar to MH in that it is a drug-induced disorder characterized by hyperthermia, muscle rigidity, and altered mentation (14,15).

Pathogenesis

NMS is the result of a decrease in dopamine-mediated transmission in the basal ganglia and hypothalamic-pituitary axis (14). As indicated in Table 43.3, NMS can be caused by drugs that inhibit dopaminergic transmission (most cases), or it can be triggered by discontinuing drugs that *facilitate* dopaminergic transmission. The drug most frequently implicated in NMS is *haloperidol* (14).

TABLE 43.3 Drugs Associated with Neuroleptic Malignant Syndrome

Drugs that Inhibit Dopaminergic Transmission	
Antipsychotic agents:	Butyrophenones (e.g., haloperidol), phenothiazines, clozapine, olanzapine, respiradone
Antiemetic agents:	Metoclopramide, droperidol, prochlorperazine
CNS stimulants:	Amphetamines, cocaine
Other:	Lithium, tricyclic antidepressants
Drugs that Facilitate Dopaminergic Transmission†	
Dopaminergic drugs:	Amantidine, bromocriptine, levodopa

†Discontinuing these drugs can trigger the neuroleptic malignant syndrome.

Despite the association with certain drugs, NMS appears in fewer than 1% of patients treated with high-risk drugs (15), and there is no relationship between drug doses and the appearance of NMS (14). It is thus an idiosyncratic reaction, rather than a dose-dependent toxic reaction.

Clinical Features

Most cases of NMS begin to appear 24 to 72 hours after the initiation of drug therapy, and almost all cases are apparent in the first 2 weeks of drug therapy. The onset is usually gradual, and the initial manifestations are muscle rigidity and agitation or confusion (14). The increase in body temperature can be delayed for 8 to 10 hours after the onset of muscle rigidity (16). Autonomic hyperreactivity is also common, and can produce tachycardia and diaphoresis (15). Severe cases are characterized by *lead-pipe rigidity*, rhabdomyolysis, and depressed consciousness.

Dystonic reactions, which are common complications of neuroleptic agents, can be difficult to distinguish from NMS, especially in the early stage of NMS, when muscle rigidity may be the only manifestation. The plasma level of creatine kinase (CK) can help in this regard, because plasma CK levels are only mildly elevated in dystonic reactions, but are typically higher than 1,000 Units/L in NMS (17).

Management

The single most important therapeutic measure is *immediate* removal of the offending drug. If NMS is caused by discontinuation of dopaminergic drugs, the drug should be restarted immediately, with gradual reduction of the drug dosage at a later time. General measures for NMS can include the following (15):

. Aggressive fluid infusion may be necessary for patients with rhabdomyolysis or hypotension.

. External cooling may be needed to reduce the body temperature, but control of the muscle

rigidity usually corrects the problem (15).

. Prophylaxis for venous thromboembolism is mandatory, because there is an increased risk of deep vein thrombosis in NMS (14).

. Benzodiazepines are often used in patients who are agitated (15,17).

Management of the muscle rigidity is possible with the following drugs:

BROMOCRIPTINE: Bromocriptine mesylate is a dopamine agonist that has been successful in treating NMS when given orally in a dose of 10 mg three times daily (15). Some improvement in muscle rigidity can be seen within hours after the start of therapy, but the *full response often takes days to develop* (18). Hypotension and hallucinations are troublesome side effects (15).

DANTROLENE: Dantrolene (the same muscle relaxant used in the treatment of MH) can be used for severe cases of NMS (when a more rapid response is desirable), although the success in clinical trials has been inconsistent (15). The optimal dosing regimen is not clearly defined, but one suggested regimen is as follows (15):

. Start with IV dantrolene in a bolus dose of 1 mg/kg every 8 hours, until symptoms resolve, or the cumulative dose reaches 10 mg/kg.

. Follow the initial regimen with oral dantrolene in a daily dose of 50–200 mg given in 3–4 divided doses.

Treatment of NMS should continue for about 10 days after clinical resolution because of delayed clearance of many neuroleptics. When depot preparations are implicated, therapy should continue for 2 to 3 weeks after clinical resolution (14).

Serotonin Syndrome

Overstimulation of serotonin receptors in the central nervous systems produces a variety of neurologic abnormalities that make up what is known as the *serotonin syndrome* (19). This syndrome has received much more attention in recent years, thanks to the popularity of serotonin reuptake inhibitors (SSRIs) for the treatment of depression.

TABLE 43.4 Drugs that can Produce the Serotonin Syndrome

Mechanism	Drugs†
Increased serotonin synthesis	L-tryptophan
Decreased serotonin breakdown	MAO inhibitors (including linezolid), ritonavir
Increased serotonin release	Amphetamines, MDMA (ecstasy), cocaine
Decreased serotonin reuptake	SSRIs, TCAs, dextromethorphan, meperidine, fentanyl, tramadol
Serotonin receptor agonists	Lithium, sumitriptan, buspirone, LSD

†See Reference 19 for a comprehensive list of drugs. Abbreviations: MAO = monoamine oxidase, MDMA = methylene dioxy-methamphetamine, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic

antidepressants.

Pathogenesis

Serotonin is a neurotransmitter that participates in sleep-wakefulness cycles, mood, and thermoregulation. A variety of drugs can enhance serotonin neurotransmission and thereby promote the serotonin syndrome, and a list of these drugs is shown in Table 43.4. Many of these drugs are mood enhancers, including illegal substances like "ecstasy", an amphetamine derivative implicated in life-threatening cases of SS (20). Note also that fentanyl and linezolid (two drugs used in the care of ICU patients) are capable of causing NMS. The serotonin syndrome occurs most often when two serotonergic drugs are used together.

Clinical Manifestations

The clinical features of serotonin syndrome (SS) can be placed in three categories: motor hyperactivity, adrenergic hyperactivity, and altered mentation. This is shown in Table 43.5, along with the frequency of clinical manifestations in each category (21). The following points about the clinical presentation of SS deserve mention:

. The clinical features that are most specific for SS are hyperreflexia, myoclonus, and clonus (spontaneous or inducible) (21,22).

. Although infrequent, *ocular clonus (spontaneous horizontal eye movements) is considered the most reliable clinical finding for the diagnosis of SS* (22).

. Mild cases of SS are often characterized by hyperreflexia, tachycardia, and agitation. Muscle rigidity appears in more severe cases, and can mask the more specific manifestations of SS (e.g., hyperreflexia).

. Although hyperthermia is considered one of the hallmarks of SS, elevated body temperatures are reported in only 60% of cases (21).

. Rhabdomyolysis is reported in 15% of cases of SS (21), and usually appears along with muscle rigidity.

TABLE 43.5 Clinical Manifestations of the Serotonin Syndrome

Category	Manifestations
Motor Hyperactivity	Hyperreflexia (57%) Myoclonus (42%) Clonus (34%) Ocular clonus (7%) Rigidity (45%) *
Adrenergic Hyperactivity	Increased Temp (60%) Tachycardia (85%) Hyper/hypotension (76%) Mydriasis (34%)

Altered Mentation	Agitation (56%) Confusion (64%) Coma (11%)

The frequency of clinical manifestation (in parentheses) are from Reference 21. (*) Clinical findings that are the most specific for serotonin syndrome.

SS VERSUS NMS: Many of the clinical features of SS are similar to NMS: i.e., both are characterized by muscle rigidity, altered mental status, increased body temperature, and adrenergic hyperactivity. The distinguishing features of SS are the hyperreflexia and clonus, but severe cases of SS (where muscle rigidity predominates and can mask the hyperreflexia and clonus) can be difficult to distinguish from NMS (15). A careful drug history is often helpful, although these two conditions share some of the causative agents.

Management

As in other drug-induced hyperthermia syndromes, removal of the precipitating drug(s) is the single most important therapeutic measure in SS. The general supportive measures in SS are the same as described for NMS. Most cases of SS resolve within days with general supportive care. Severe cases of SS can benefit from a serotonin antagonist like cyproheptadine.

CYPROHEPTADINE: Cyproheptadine is a serotonin antagonist that is available for oral administration only, but tablets can be broken up and administered through a nasogastric tube. The initial dose is 12 mg, followed by 2 mg every 2 hrs for persistent symptoms, and the maintenance dose is 8 mg every 6 hours (15). This drug is sedating, but that can benefit the agitation in SS.

PARALYSIS: Severe rigidity and rhabdomyolysis that does not improve with conventional measures may require neuromuscular paralysis with a nondepolarizing agent (e.g., rocuronium).

HYPOTHERMIA

Hypothermia is defined as a body temperature <35° C (<95° F), and can be either primary (i.e., the result of environmental conditions), secondary (i.e., triggered by illness or trauma), or therapeutic (i.e., targeted temperature management). The focus of this section is primary (environmental) hypothermia.

Pathogenesis

Physiologically, the human body is better equipped to survive in hot rather than cold environments. The physiological response to cold includes *cutaneous vasoconstriction* (to reduce convective heat loss) and *shivering* (which can double metabolic heat production), but these physiological responses provide protection only in the early stages of hypothermia. Instead, the behavioral responses to cold (e.g., wearing warm clothing or seeking shelter from the cold) play a major role in the adaptation to cold.

Predisposing Conditions

Environmental hypothermia is most likely to occur in the following situations:

. Immersion in cold water (<15° C or <59° F) can be fatal after 30 minutes (23), because heat loss to cold water occurs much more rapidly than heat loss to cold air. This is also why exposure to cold in wet clothing predisposes to hypothermia.

. Windy conditions promote hypothermia in cold environments, because wind promotes heat loss by convection (as described earlier). This is the basis for the wind-chill index, which describes the combined effect of ambient temperature and wind speed on the temperature at the skin surface (24).

. Hpothermia is a risk when the behavioral responses to cold are impaired; e.g., by alcohol or drug intoxication.

Clinical Presentation

The clinical manifestations in progressive hypothermia are summarized in Table 43.6 (23,25).

TABLE 43.6 Manifestations of Progressive Hypothermia

Severity	Body Temp	Clinical Manifestations
Mild	32–35° C 90–95° F	Confusion, cold and pale skin, shivering, tachycardia
Moderate	28–31.9° C 82–89.9° F	Lethargy, reduced or absent shivering, bradycardia, bradypnea
Severe	<28° C <82° F	Obtundation or coma, no shivering, dilated and fixed pupils, bradycardia, hypotension, oliguria, edema
Fatal	<24° C <75° F	Apnea, asystole

Mild Hypothermia

Mild hypothermia is defined as a body temperature of 32–35° C (90–95° F). At this stage, patients are often confused, but they shows signs of adaptation to cold; i.e., the skin is pale and cold from cutaneous vasoconstriction, and shivering is brisk. Tachycardia also predominates at this stage, and the blood pressure can be elevated (26).

Moderate Hypothermia

Patients with moderate hyperthermia (i.e., 28–31.9° C or 82–89.9° F) are lethargic, and shivering may be present if the body temperature is above 30° C (23). Bradycardia and a decreased respiratory rate (bradypnea) predominate at temperatures below 32° C (26).

Severe Hypothermia

Patients with severe hypothermia (<28° C or <82° F) are usually obtunded or comatose, and have dilated, fixed pupils. Additional findings include hypotension, severe bradycardia, oliguria, and generalized edema.

Apnea and asystole are expected at body temperatures below 24° C (75° F), but *the diagnosis*

of death cannot be made in the setting of hypothermia (25,26). The body must be warmed to a normal temperature before the pronouncement of death. (See also the brain death determination in Chapter 45).

Diagnostic Evaluation

Exposure to a cold environment results in skin temperatures that are lower than interior (core) temperatures, so peripheral temperature measurements (i.e., oral, axillary, temporal artery, and tympanic temperatures) are not appropriate in hypothermic patients (27). Core temperature measurements are advised, using bladder, esophageal, or rectal probes.

Laboratory Evaluation

The following points deserve mention concerning the laboratory evaluation of hypothermic patients:

. Arterial blood gas measurements (which are performed at 37° C) should be adjusted to the patient's body temperature (26). In moderate-to-severe hypothermia, expect a combined respiratory and metabolic acidosis.

. Serum electrolytes can reveal hyperkalemia, from potassium release by skeletal muscle, as a result of shivering and/or rhabdomyolysis.

. Serum creatinine levels can be elevated as a result of rhabdomyolysis, acute renal failure, or *cold diuresis* (caused by diminished renal tubular responsiveness to antidiuretic hormone).

. A generalized coagulopathy (i.e., thrombocytopenia, and prolongation of the prothrombin time and partial thromboplastin times) is common at temperatures below 34° C (93° F) (26), but may not be evident if the coagulation profile is run at normal body temperatures (28).

Electrocardiogram

The electrocardiogram in hypothermia can show positive J (Osborn) waves at the junction between the QRS complex and the ST segment (see Figure 43.1), especially in leads II and V6 (26). These *Osborn waves* are not specific for hypothermia, and can occur with hypercalcemia, subarachnoid hemorrhage, cerebral injuries, and myocardial ischemia (29). Despite the attention these waves have received, they are merely a curiosity, and have little or no diagnostic or prognostic value in hypothermia.

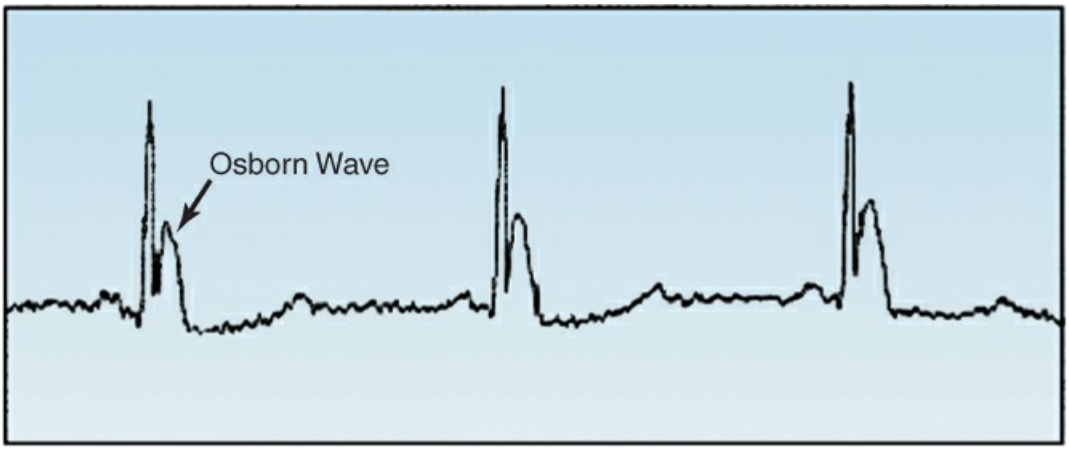

FIGURE 43.1 The (overhyped) Osborn wave.

ARRHYTHMIAS: The threshold for atrial and ventricular arrhythmias is reduced at temperatures below 32° C (90° F), and there is also a progressive bradycardia at temperatures <32° C that is resistant to atropine. Finally, there is a risk of ventricular fibrillation and asystole at temperatures below 28° C (82.4° F) (26).

Rewarming

There are several approaches to rewarming, depending on the severity of the hypothermia.

External Rewarming

External rewarming is adequate for most cases of hypothermia Passive rewarming (e.g., removing wet clothes, covering the patient in blankets) prevents heat loss, and allows the patient's body to rewarm physiologically. Active warming (e.g., with heating pads or automated warming systems) prevents heat loss and accelerates warming.

Internal Rewarming

Internal rewarming is generally reserved for severe cases of hypothermia where active external warming is ineffective. The following are some relevant points about internal rewarming:

. For intubated patients, heating the inhaled gases to 40–45° C (104–113° F) can raise the core temperature 2.5° C per hour (28).

. Heated IV fluids prevent further cooling, but they do not promote rewarming (23).

. Internal rewarming methods that are not recommended include gastric lavage with heated fluid (risk of aspiration), and warmed bladder lavage (ineffective) (23).

. For hypothermic cardiac arrest, venoarterial ECMO has been used successfully (30).

Volume Resuscitation

Patients with moderate-to-severe hypothermia are often volume depleted (from cold diuresis), and the vasodilation that accompanies rewarming promotes hypotension. Therefore, attention to fluid infusion is needed during the rewarming process. However, the infusion of fluids at room temperature (21° C or 70° F) promotes further cooling, so the infused fluids should be heated.

Patients who are refractory to volume infusion should be considered for venoarterial ECMO, if available.

A FINAL WORD

The Adaptable Human

One of the notable features of heat-related illness and accidental hypothermia is the relatively low number of fatalities. For example, there were an average of 702 deaths yearly in the United States from heat-related illness over the years from 2004 to 2018 (31), compared to 695,000 deaths yearly from heart disease (32), and a 10-year survey in New York City (from 2009 to 2019) showed only 139 deaths from hypothermia, with an annualized death rate of 1.7 per million (33). These relatively small numbers are a testament to the ability of humans to adapt (both physiologically and behaviorally) to environmental extremes.

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Chapter 44

Fever in the ICU

Give me the power to produce fever, and I will cure all diseases.

Parmenides (ca. 500 B.C.)

The appearance of a new fever is always a matter of concern in a hospitalized patient. This chapter presents a practical approach to a new-onset fever in the ICU, and includes the preferred methods of measuring body temperature and obtaining blood cultures, and the most likely sources of fever in ICU patients, both noninfectious and infectious (1). The final section of the chapter focuses on the practice of suppressing fever, and why Parmenides would disapprove of this practice.

FEVER BASICS

Two scales (Celsius and Fahrenheit) are used to record body temperature, and the conversion from one scale to the other is shown in Table 44.1. Readings on the Celsius scale are often called "degrees centigrade", but this unit is intended for the degrees on a compass, not for temperatures (2).

Thermometry

. The preferred method of measuring body temperature is a thermistor-equipped catheter placed in either the pulmonary artery, esophagus, or urinary bladder (1). These catheters provide the most accurate measure of core body temperature, and they also allow continuous temperature monitoring.

. If the above methods are not available, then oral or rectal temperatures are preferred (1). However, oral temperatures can be 0.5° C (0.9° F) lower than core body temperatures in patients with tachypnea (3).

. Peripheral temperature measurements (i.e., tympanic membrane, temporal artery, and axillary temperatures) do not have clinically acceptable accuracy (4), and should not be used to make decisions based on the body temperature.

Definition of Fever

The body temperature has a diurnal variation, with the nadir in the early morning (between 4 and 8 AM) and the peak in the late afternoon (between 4 and 6 PM). The range of diurnal variation varies for each patient, and can be as high as 1.3° C (2.4° F) (5). Fever is best defined as a temperature that exceeds the normal diurnal variation for each patient, but this is not useful clinically (since the diurnal variation for each patients is usually not known). The following definitions of fever are included in the most recent clinical practice guidelines on fever in the ICU (1):

. In ICU patients, a single temperature measurement of 38.3° C (101° F) or higher represents a fever, and deserves further evaluation.

. A lower threshold of 38.0° C (100.4° F) can be used for neutropenic patients if the temperature elevation is sustained for at least one hour.

TABLE 44.1 Converting Celsius and Fahrenheit Temperatures

°C	°F	Conversion Formulas
100	212	Conversions are based on the corresponding temperatures at the freezing point of water,
40	104	0° C = 32° F
39	102.2	and the corresponding temperature ranges from freezing point to boiling point of water,
38	100.4	Δ100° C = Δ180° F
37	98.6	which can be reduced to:
36	96.8	Δ5° C = Δ9° F
35	95	These relationships are then combined to derive the following formulas:
34	93.2	0° F = (9/5° C) + 32°
33	91.4	0° C = 5/9 (° F – 32°)
0	32	

The Febrile Response

Fever is the result of inflammatory cytokines (called endogenous pyrogens) that act on the hypothalamus to elevate the body temperature. Therefore, any condition that triggers a systemic inflammatory response will produce a fever. Some implications of the febrile response are stated below.

. *Fever is a sign of inflammation, not infection*, and about 50% of ICU patients who develop a fever have no evidence of infection (6,7).

. The presence or severity of fever does not correlate with the presence or severity of infection. High fevers can be the result of a noninfectious process, while fever can be absent in life-threatening infections.

The distinction between inflammation and infection is an important one, not only for the evaluation of fever, but also for curtailing the unnecessary use of antibiotics.

Fever as an Adaptive Response

Whereas hyperthermia is the result of abnormal temperature regulation (see Chapter 43), fever is

characterized by a normal thermoregulatory system that is operating at a higher set point (8). The consensus view is that fever is not a pathological condition, but rather is an adaptive response that enhances inherent defenses against infection (9). The beneficial effects of fever are described later in the chapter.

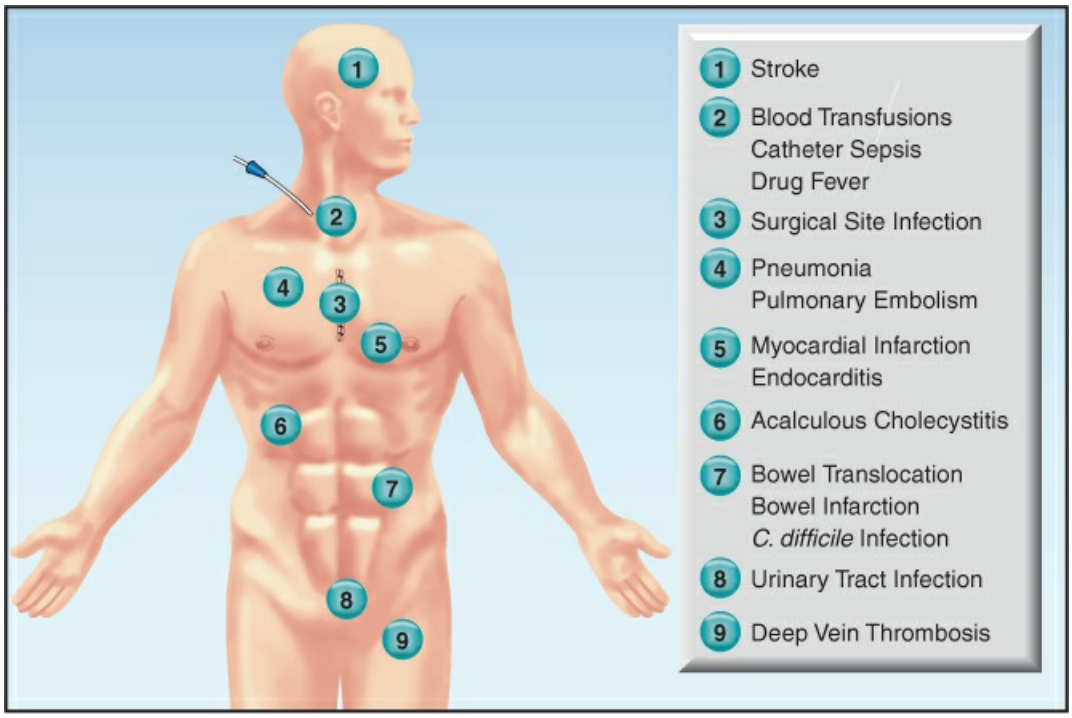

FIGURE 44.1 Potential sources of new-onset fever in the ICU.

Sources of Fever

Any condition capable of triggering an inflammatory response is capable of causing a fever. The notable sources of nosocomial fever in the ICU are shown in Figure 44.1.

NONINFECTIOUS SOURCES OF FEVER

As mentioned earlier, infection is responsible for only half of ICU-acquired fevers (6.7). The noninfectious conditions listed in Table 44.2 are responsible for most of the remaining fevers.

TABLE 44.2 Noninfectious Causes of Fever in the ICU

More Common	Less Common
Early Postoperative Fever	Adrenal Insufficiency
Venous Thromboembolism	Bowel Infarction
Drug Fever	Dressler Syndrome
Blood Transfusions	Fat Embolism
Myocardial Infarction	Tumor Lysis Syndrome
Alcohol/Drug Withdrawal	Malignant Hyperthermia
Inflammatory Lung Injury	Serotonin Syndrome

Ischemic Stroke	Iatrogenic Fever

Early Postoperative Fever

Major surgery is a source of tissue injury. Because inflammation and fever are the normal response to tissue injury, it is no surprise that fever in the first postoperative day is reported in 15–40% of cases of major surgery (10–12). In most cases, there is no evidence of infection (10,11), and the fever resolves in 24 to 48 hours.

Atelectasis Does NOT Cause Fever

There is a longstanding misconception that atelectasis is responsible for early postoperative fevers. One possible source of this misconception is the high incidence of atelectasis in patients who develop a postoperative fever. This is demonstrated in Figure 44.2 (see the graph on the left), which is from a study involving patients who underwent open heart surgery (12). Close to 90% of the patients with a fever on the first postoperative day had radiographic evidence of atelectasis. This, however, is *not* evidence that the atelectasis is the source of fever. In fact, the graph on the right in Figure 44.2 shows that most (75%) of the patients with atelectasis did not have a fever. The inability of atelectasis to produce fever was demonstrated over 50 years ago in an animal study where lobar atelectasis produced by ligation of a mainstem bronchus was not accompanied by fever (13).

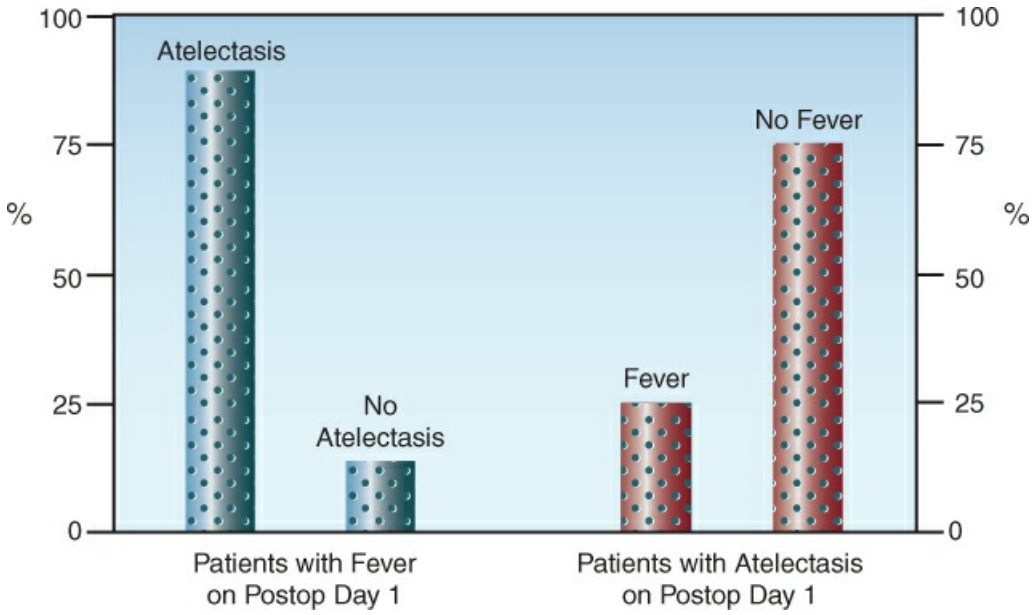

FIGURE 44.2 The relationships between fever and atelectasis in the first postoperative day following open heart surgery for 100 patients. The graph on the left shows that most patients with fever had atelectasis, but the graph on the right shows that most patients with atelectasis did not have a fever. Data from Reference 12.

To summarize, atelectasis is a common complication of major surgery, and occurs in over 90% of cases of general anesthesia (14). However, it is not a common cause of postoperative fever. *Most fevers that appear in the first 24 hours after surgery are the result of the tissue injury sustained during the procedure.*

Malignant Hyperthermia

An uncommon but treatable cause of elevated body temperatures in the immediate postoperative period is *malignant hyperthermia* (15), an inherited disorder characterized by hyperpyrexia (temperature >104° F), muscle rigidity, and rhabdomyolysis in response to halogenated inhalational anesthetics. This disorder is described in Chapter 43.

Venous Thromboembolism

There are numerous risk factors for venous thromboembolism in ICU patients (see Table 5.1 and Figure 5.1), but the risk is highest in trauma victims and postoperative patients. Hospital-acquired deep vein thrombosis is usually asymptomatic, but acute pulmonary embolism can produce a fever that lasts for one week (16). The diagnostic approach to acute pulmonary embolism is described in Chapter 22.

Blood Transfusions

Transfusions of red blood cells (RBCs) and platelet products can trigger febrile reactions.

RBC Transfusions

Nonhemolytic fever is the most common adverse reaction to RBC transfusions (see Table 12.5), and usually appears during the transfusion, or within 6 hours after the transfusion is completed. These reactions are the result of antileukocyte antibodies in the recipient that react with donor leukocytes, and they are more likely to occur in patients who have received multiple transfusions.

Platelet Transfusions

Nonhemolytic fever is one of the more cited adverse reactions to platelet transfusions, especially with single-donor platelets (see Table 13.4). However, these reactions are infrequent (e.g., about one per 1,000 units transfused for single-donor platelets) (17).

Drug Fever

Drug-induced fever is typically a hypersensitivity reaction, but can also be an idiosyncratic reaction. Any drug can potentially trigger a febrile response, but the ones reported most frequently are listed in Table 44.3 (18,19).

There is no standard description for drug fever. The onset of the fever varies from a few days to more than a month after the start of drug therapy, and the fever can appear as an isolated finding, or it can be accompanied by the other manifestations listed in Table 44.3 (20). Note that about half of the patients have rigors, and about 20% develop hypotension, indicating that *patients with a drug fever can appear to be seriously ill*. Evidence of a hypersensitivity reaction (i.e., eosinophilia and rash) is absent in over 75% of cases of drug fever (20).

TABLE 44.3 Drug-Associated Fever

Common Offenders[a]	Clinical Findings[b]
Amphotericin	Rigors (53%)

Carbamazepine	Myalgias (25%)
Cephalosporins	Leukocytosis (22%)
Heparins	Eosinophilia (22%)
Penicillins	Rash (18%)
Phenytoin	Hypotension (18%)
Procainamide	
Quinidine	

[a]For a more complete list, see Reference 18. [b]From Reference 20.

Suspicion of drug fever usually occurs when there are no other likely sources of fever. When suspected, possible offending drugs should be discontinued, and the fever should disappear within 72 hours (18).

Other Sources

The following are other some noninfectious causes of fever that deserve mention:

. Severe withdrawal from alcohol, opiates, benzodiazepines, barbiturates, and possibly gabapentin, can cause a fever that typically appears a few days after abstinence.

. Adrenal insufficiency is a recognized cause of fever, and can be the result of spontaneous adrenal hemorrhage from anticoagulant therapy or disseminated intravascular coagulation (DIC). The diagnosis of adrenal insufficiency is described in Chapter 51.

. Acute respiratory distress syndrome (ARDS) is an inflammatory lung injury from multiple sources that can produce a fever. This condition is described in detail in Chapter 24.

. Infarctions of the heart, brain, and bowel are potential sources of fever.

. The serotonin syndrome, which is accompanied by fever, can be a complication of treatment with critical care drugs like fentanyl, tramadol, and linezolid (see Table 43.4).

Iatrogenic Fever

Faulty thermal regulators in water mattresses and aerosol humidifiers can cause fever by transference (21). It takes only a minute to check the temperature settings on heated mattresses and ventilators, but it can take far longer to explain why such a simple cause of fever was overlooked.

NOSOCOMIAL INFECTIONS

The major ICU-acquired infections are pneumonias (especially ventilator-associated pneumonias), bloodstream infections from vascular catheters, urinary tract infections, surgical site infections, and *Clostridium difficile* infections: Table 44.4 shows the number of each of these infections reported in the United States over a one-year period (22). All but one of these infections is described elsewhere in the book: i.e., catheter-related bloodstream infections are described in Chapter 3, ventilator-associated pneumonia in Chapter 29, *C. difficile* infections in Chapter 41, and urinary tract infections in Chapter 42.

Surgical Site Infections

Surgical site infections (SSIs) continue to be a significant source of postoperative morbidity despite a long history of preventive efforts. These infections typically appear 5–7 days after surgery, but any wound infection that develops within 30 days following surgery is classified as an SSI (23). Infected wounds are identified by signs of local inflammation (erythema, edema, tenderness), and by purulent or foul-smelling drainage. Superficial infections are less likely to produce fever than infections with deep tissue involvement.

There are multiple risk factors for SSIs, including the condition of the patient and the type of procedure. The reported incidence of SSIs is 1–2% following clean procedures (where the chest or abdomen is not opened), and 4–5% following contaminated procedures (e.g., bowel perforation with soilage of the peritoneal cavity) (24). The pathogens involved in SSIs are also determined by the surgical procedure: e.g., SSIs from clean surgical procedures usually involve *Staphylococcus aureus*, while SSIs from contaminated procedures often involve gram-negative aerobic bacilli (24).

TABLE 44.4 Hospital-Acquired Infections in the United States in 2021

Infection	Total #	# in ICUs
Ventilator-Associated Events	50,050	47,254
C. difficile Infection	44,948	—
Catheter-Associated Bloodstream Infection	27,021	14,003
Catheter-Associated Urinary Tract Infection	24,710	12,208
Surgical Site Infection	21,186	—

*A ventilator-associated event is a respiratory infection (tracheobroncitis or pneumonia) that appears after 48 hours of mechanical ventilation, and results in an increased requirement for inhaled O_2 or PEEP. Data from Reference 21.

Management

Management of SSIs includes debridement, with antibiotics added if there is a fever. For initial antibiotic coverage, vancomycin is appropriate if *Staphylococcus aureus* is suspected, and for contaminated procedures (e.g., abdominal surgery), either *piperacillin/tazobactam*, or a third generation cephalosporin (e.g., *ceftriaxone*) plus *metronidazole* is advised (25).

Necrotizing Wound Infections

Necrotizing wound infections are evident in the first few postoperative days. Early signs include marked erythema and edema, and *pain that is out of proportion to the skin changes* (due to ischemic nerve injury) (26). Crepitance and skin blistering are later findings. Spread to deeper structures (with rhabdomyolysis) is rapid, and a milky or foul-smelling discharge may be evident (from the underlying necrosis). These infections can be caused by a single organism (usually β-hemolytic streptococci or *Clostridium* species), or they can be polymicrobial (usually a mix of gram-negative enteric organisms and anaerobes) (26).

MANAGEMENT: *Emergent and extensive debridement is mandatory for survival*, along with appropriate antibiotic therapy. A Gram stain can help with the initial antibiotic selection. If

streptococci or clostridial organisms are suspected, the appropriate regimen is *penicillin plus clindamycin*, and if the surgery involved the deep structures in the abdomen or thorax, then a carbapenem (e.g., *meropenem*) is advised (25).

Other Considerations

The following are infections that should be considered in specific situations.

Endocarditis

Nosocomial endocarditis is uncommon, but an evaluation for endocarditis is indicated in the following situations:

. Any patient with bacteremia involving streptococci, staphylococci, or enterococci, who also has an abnormal or prosthetic heart valve.

. All patients with blood cultures growing *Staphylococcus aureus*, regardless of the condition of the heart valves.

DIAGNOSIS: Echocardiography is the standard method used to diagnose endocarditis. The evaluation can begin with *transthoracic echocardiography* (TTE), which is easily obtained at the bedside. However, TTE has a limited sensitivity for the detection of vegetations on native valves (sensitivity of 60%–70%), and especially on prosthetic valves (sensitivity of 50%) (27), so a negative TTE must be followed by *transesophageal echocardiography* (TEE), which has a sensitivity of at least 90% for the detection of vegetations on native and prosthetic valves (27).

THERAPY: The antimicrobial therapy for endocarditis has several variations (depending on the infecting organism, patterns of resistance, and the involvement of a native or prosthetic valve), and it is a prolonged affair that can be marred by complications (e.g., emboli) (28). It thus seems wise to have an infectious disease specialist guide the treatment of these infections.

Peritoneal Infections

. Peritonitis or intra-abdominal abscess should be suspected in any patient who has had extensive or contaminated abdominal surgery and has a persistent or late-onset (one week or later) postoperative fever. These infections are described in Chapter 41.

. Spontaneous bacterial peritonitis is a consideration in any patient with cirrhosis and ascites who develops an unexplained fever. This infection is described in Chapter 39.

Disseminated Candidiasis

Risk factors for disseminated candidiasis include indwelling central venous catheters, recent abdominal surgery, or recent exposure to broad spectrum antibiotics. Most ICU patients have at least one of these risk factors, so *disseminated candidiasis should be considered in the following situations*:

. Any ICU patient with persistent fever of unclear etiology.

. A patient with a *Candida* urinary tract infection.

DIAGNOSIS: Disseminated candidiasis is a challenging diagnosis because ICU patients are often colonized with *Candida* species, and the sensitivity of blood cultures for the detection of invasive *Candida* infections is as low as 20% (29). However, *a polymerase chain reaction (PCR)-based test is commercially available that can detect Candida species in blood with a sensitivity and specificity >90%* (30), and this test should be considered (if available) for patients with possible invasive candidiasis. Persistent candiduria or a *Candida* urinary tract infection is usually a consequence of disseminated candidiasis (31), so this can be a valuable sign of invasive disease.

ANTIFUNGAL TREATMENT: About half of the cases of disseminated candidiasis are due to *Candida* species other than *Candida albicans*, so fluconazole is not appropriate for empiric coverage. Instead, empiric antifungal coverage should include an echinocandin (i.e., *micafungin, caspofungin,* or *anidulafungin*) or *amphotericin* for severely ill patients.

GENERAL CONSIDERATIONS

The evaluation of fever can travel many roads, but the following measures are included in most evaluations.

Blood Cultures

Blood cultures are recommended for all cases of ICU-related fever where an infection is possible. The yield from blood cultures is dependent on the volume of blood withdrawn during a venipuncture, and the number of venipuncture sites.

Influence of Volume

The yield from blood cultures is optimal when 20–30 mL of blood is withdrawn from each venipuncture site (32). The standard practice is to withdraw 20 mL of blood from a venipuncture site: one-half (10 mL) is then injected into each of the two bottles of broth (one aerobic and one anaerobic) provided in a blood culture set. Increasing from 20 ml to 30 mL of blood increases the yield from blood cultures by about 10% (33). When using 30 mL per venipuncture, the extra 10 mL aliquot of blood should be injected into the aerobic broth bottle (33).

Number of Blood Cultures

The relationship between the number of blood cultures and the detection of bacteremia is shown in Figure 44.3 (34). (*Note:* The number of blood cultures represents the number of venipuncture sites.) This is from a study of patients with bacteremia documented by four or more blood cultures drawn over a 24 hour period. Note that the majority of the bacteremias (94%) were detected with two blood cultures in the patients with endocarditis, while three blood cultures were required to detect over 90% of the bacteremias in patients with other infections. This data is the basis for the following recommendations:

. Three to four blood cultures drawn over a 24-hour period is recommended for the optimal detection of bacteremia (1).

. Two blood cultures are satisfactory for detecting bacteremia in cases of endocarditis.

The bacteremia in endocarditis is continuous, which may explain why fewer blood cultures are needed to detect bacteremia.

Multilumen Catheters

The following recommendation pertains to the evaluation of possible catheter-related septicemia with multilumen central venous catheters (1).

. For multilumen catheters, separate blood cultures should be drawn through two lumens of the catheter, along with a blood culture from a peripheral venipuncture site. *Note:* Cultures from a single port can miss as many as 40% of catheter-related infections (35).

. If the same organism is isolated in catheter and peripheral blood, then the "time to positivity" is compared. When growth in catheter blood appears at least two hours before growth in peripheral blood, the diagnosis is catheter-related septicemia.

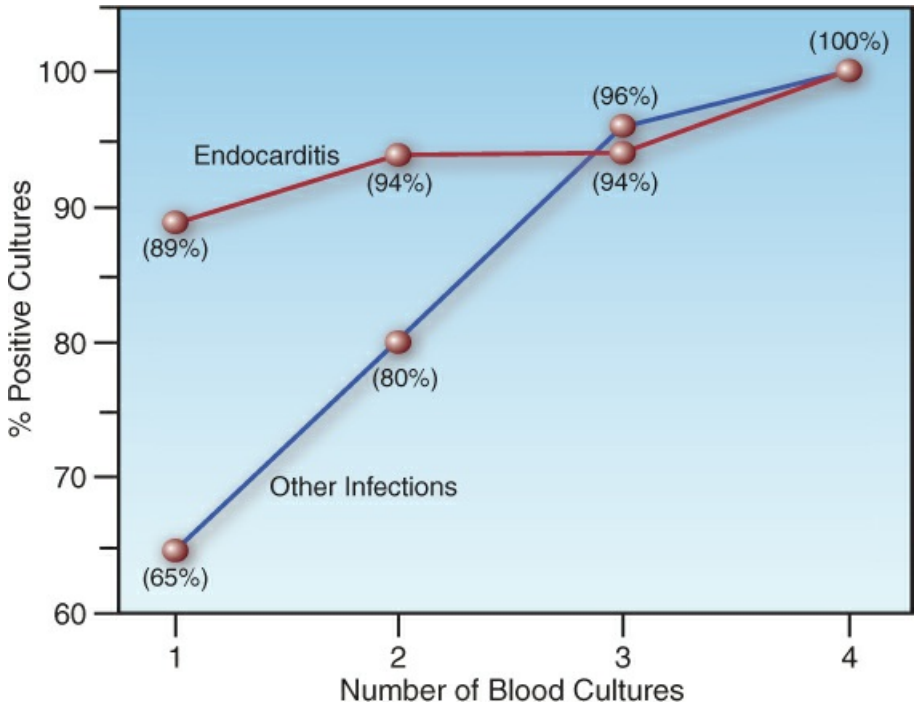

FIGURE 44.3 Relationship between the number of blood cultures drawn over a 24 hour period (20 mL per blood culture) and the detection rate for bacteremia. See text for explanation. Data from Reference 34.

Each lumen of a multilumen catheter is a potential source of septicemia (36). so the optimal strategy would be to culture all ports of the catheter. (The diagnosis of catheter-related septicemia is described in detail in Chapter 3.)

Molecular Testing

Growth in blood cultures often takes 48 hours or longer to detect, which has disadvantages (e.g., it delays treatment with appropriate antibiotics when cultures are positive, and promotes the overuse of antibiotics when cultures are negative). More rapid detection of organisms in the bloodstream is possible using DNA amplification (like the PCR method mentioned earlier for

detecting candidemia), and a commercially available product is available (T2Bacteria® Panel, T2Biosystems, Lexington MA) that can detect six bacterial species (*E. coli, P. aeruginosa, K. pneumoniae, S. aureus, E. faecium*, and *A. baumannni*) with a sensitivity and specificity of 90% (37). Results can be available in 3–5 hours.

The value of the rapid detection methodology for improving outcomes has yet to be determined, but seems questionable, since a positive test still requires culture results for antibiotic sensitivities, and a negative test does not rule out infection with other organisms.

Empiric Antimicrobial Therapy

Empiric antibiotic therapy is recommended when the likelihood of infection is high. Prompt initiation of antimicrobial therapy is considered essential, *particularly in patients with neutropenia* (absolute neutrophil count <500), where delays of only a few hours can have a negative impact on outcomes (38).

Empiric antibiotic coverage is described elsewhere in the book for ventilator-associated pneumonia (see Table 29.6), catheter-related bloodstream infections (see Table 3.6), catheter-associated urinary tract infections (see Chapter 42), and surgical site infections (see earlier in this chapter). The following are some general statements about empiric antibiotics for ICU-related fever.

. Most ICU-related infections are caused by *Staphylococcus aureus*, or bowel microbes (e.g., *E. coli, P. aeruginosa, C. difficile, Enterococcus* spp).

. Empiric coverage for the major ICU-related infections (i.e., pneumonia, vascular catheter infections, urinary tract infections, postop abdominal infections) should include an antibiotic that is active against gram-negative aerobic bacilli. Popular choices are *piperacillin/tazobactam, cefepime,* or *meropenem*.

. Coverage for *S. aureus* should be included for suspected catheter-related infections and ventilator-associated pneumonia. Vancomycin is a popular choice because it covers both methicillin-resistant and methicillin-sensitive strains of *S. aureus*.

. An antifungal agent should be considered for patients who have a risk of invasive candidiasis (e.g., those with central venous catheters) who also have: (*a*) persistent fever of unclear etiology, (*b*) fever following contaminated bowel surgery, or (*c*) fever associated with persistent candiduria. An agent that covers all *Candida* species (such as an echinocandin) is most appropriate.

ANTIPYRETIC THERAPY

The popular perception of fever as a malady that must be corrected is rooted in hearsay. In fact, it seems that *fever is a normal adaptive response that enhances the ability to eradicate infection* (9). This section contains some observations about fever that are intended to make you think twice about starting antipyretic therapy in critically ill patients.

Fever as a Host Defense Mechanism

An increase in body temperature can enhance immune function by increasing the production of

antibodies and cytokines, activating T-lymphocytes, facilitating neutrophil chemotaxis, and enhancing phagocytosis by neutrophils and macrophages (39,40). Fever also inhibits bacterial growth and viral replication. This is demonstrated in Figure 44.4 (41), which shows that an increase in temperature of 4° C completely suppresses growth of the microorganism.

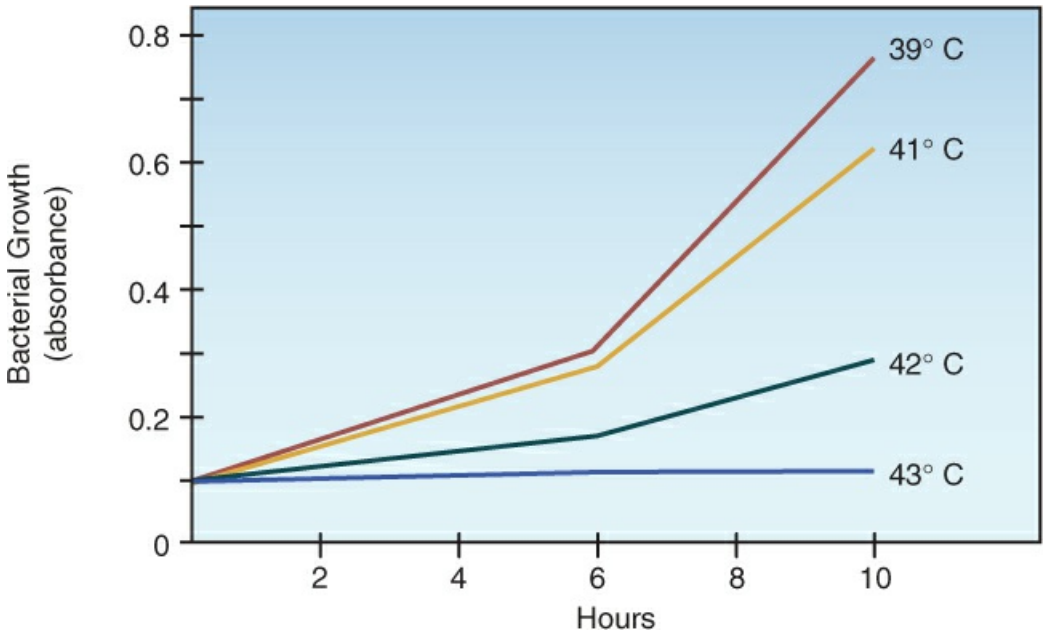

FIGURE 44.4 The influence of body temperature on the growth of *Pasteurella multocida* in the blood of infected laboratory animals. The range of temperatures in the figure is the usual range of febrile temperatures for the study animal (rabbits). Data from Reference 41.

Clinical Studies

The benefits of fever as a host defense against infection is supported by clinical studies showing an inverse relationship between body temperature and survival in patients with severe sepsis and septic shock (42–44). The results of one of these studies is shown in Figure 44.5. In this case, the initial body temperature showed an inverse relationship with in-hospital mortality in patients admitted to the ICU with severe sepsis or septic shock (42).

Similar results have been reported in other studies (43,44), including a study that showed a higher mortality rate in septic patients who received antipyretic therapy (45).

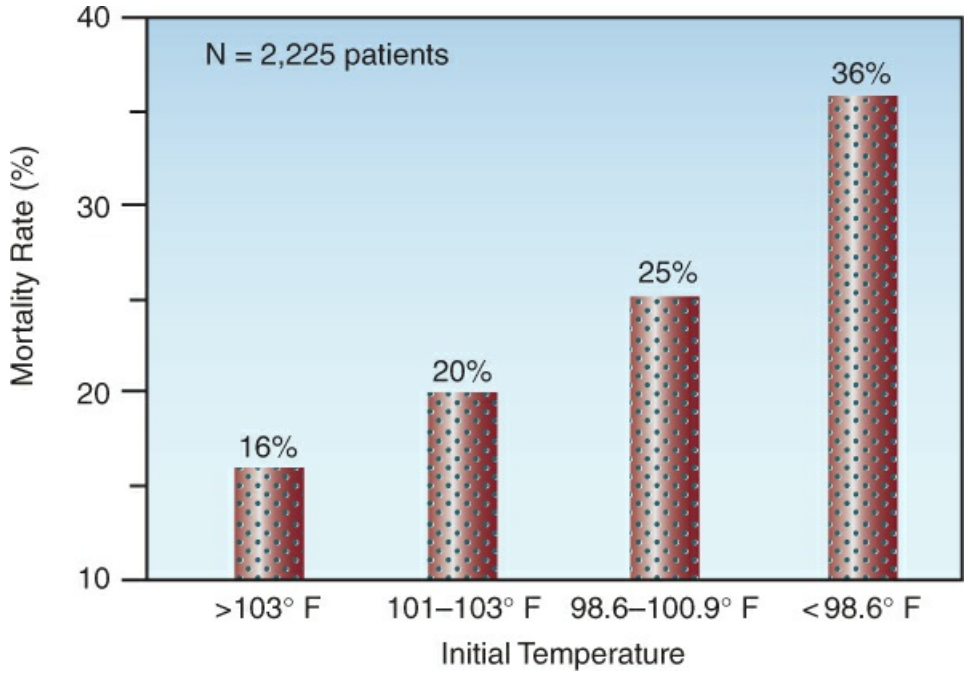

FIGURE 44.5 Inverse relationship between body temperature and in-hospital mortality rate in 2,225 patients with severe sepsis and septic shock. Differences between categories are significant at the p<0.001 level. Data from Reference 42.

THERAPEUTIC HYPERTHERMIA: The evidence of improved outcomes with fever has prompted a study in which afebrile patients with sepsis were treated with external warming to raise their body temperature by 1.5° C, and this resulted in a significant decrease in the mortality rate when compared to afebrile patients who were not warmed (46).

Summation

The available evidence shows that fever is not a pathological condition, but rather is normal adaptive response that serves an antimicrobial defense mechanism. The changing perception of fever is evident in the most recent clinical practice guidelines on fever in the ICU, which recommends not suppressing fever as a routine practice (1).

Note: It is important to mention that fever *can* be harmful (and thus should be suppressed) in patients with ischemic brain injury from a cardiac arrest or acute stroke.

Antipyretic Drugs

Prostaglandin E mediates the febrile response to endogenous pyrogens, and drugs that interfere with prostaglandin E synthesis are used as antipyretic agents. These drugs include aspirin, acetaminophen, and nonsteroidal anti-inflammatory agents (NSAIDs), but only the latter two are used for antipyresis in the ICU.

Acetaminophen

Acetaminophen is an effective antipyretic agent in critically ill patients (47), and is the most popular drug used for fever suppression in ICUs.

DOSING REGIMENS: Acetaminophen can be given orally or by rectal suppository in a dose of 650 mg every 6 hours, and an intravenous preparation is available that can be given in a dose of 650 mg every 6 hours, or 1,000 mg every 8 hours. *Caution:* Acetaminophen is hepatotoxic, and *the maximum daily dose that is considered safe is 3 grams* (FDA announcement, January 13, 2011). The drug is contraindicated in patients with hepatic insufficiency. (Acetaminophen hepatotoxicity is described in Chapter 52.)

NSAIDs

Two NSAIDs have been evaluated for fever suppression in critically ill patients: *ibuprofen* and *ketorolac*. Ibuprofen is effective in an intravenous dose of 10 mg/kg, up to 800 mg every 6 hours (48), and ketorolac is effective in a single intravenous dose of 0.5 mg/kg (49). There is a limited experience with NSAIDs in the ICU, largely due to an exaggerated fear of renal toxicity and GI hemorrhage from the use of these drugs.

Cooling Blankets

External cooling is a popular antipyretic measure, but is counterproductive in the setting of fever. The febrile response raises the body temperature by promoting cutaneous vasoconstriction and increasing skeletal muscle activity (via rigors and shivering). This is what the body normally does in response to a cold environment, so the febrile response mimics the physiological response to cold. Stated another way, *the febrile response makes the body behave like it is wrapped in a cooling blanket*. Adding a cooling blanket will only aggravate the cutaneous vasoconstriction and increased muscle activity (via shivering) that produces the fever. Cooling blankets are more appropriate for heat stroke, where the thermoregulatory response to a warm environment is lost.

A FINAL WORD

The 1927 Nobel Prize

The 1927 Nobel Prize in Medicine was awarded to Julius Wagner-Jauregg (an Austrian physician) for his discovery of the therapeutic benefits of fever in patients with neurosyphilis. Warner-Jauregg had observed that remissions in dementia paralytica (neurosyphilis) were often preceded by a febrile illness, and he subsequently performed a bold experiment where he inoculated 9 neurosyphilis patients with tertian malaria (to induce a recurrent fever). Surprisingly, 6 of the 9 patients experienced extensive remissions, with almost complete resolution of symptoms in 3 patients (50). These results were corroborated in other patients, along with the discovery that spirochetes disappeared from brain tissue during the periods of fever, and reappeared when the fever subsided.

The practice of inoculating patients with malaria to treat neurosyphilis was eventually abandoned, because it introduced a disease to treat a disease. Unfortunately, the implications of Wagner-Jauregg's work (i.e., that fever can eradicate infection) were also abandoned.

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A Final Word

50. Julius Wagner-Jauregg, Nobel Lecture: “The treatment of dementia paralytica by malaria inoculation”. December 13, 1927. (Available at www.nobelprize.org).

Section XIV

NERVOUS SYSTEM DISORDERS

There is no delusion more damaging than to get the idea in your head that you understand the functioning of your brain.

Lewis Thomas
1983

Chapter 45

Disorders of Consciousness

I think, therefore I am.

René Descartes (1644)

The ability to recognize and interact with the surroundings (i.e., consciousness) is the *sine qua non* of the life experience, and loss of this ability is one of the dominant (and dreaded) signs of a life-threatening illness. This chapter describes the major disorders of consciousness that you will encounter in the ICU, with emphasis on delirium, coma, and the ultimate disorder of consciousness, brain death.

ALTERED CONSCIOUSNESS

Consciousness has two components: arousal and awareness.

. *Arousal* is the ability to experience your surroundings, and is also known as *wakefulness*.

. *Awareness* is the ability to understand your relationship to your surroundings, and is also known as *responsiveness*.

These two components can be used to classify the altered states of consciousness, as indicated in Table 45.1 (1–3).

TABLE 45.1 Altered States of Consciousness

Can be Awakened and is Aware	Can be Awakened but is Not Aware	Cannot be Awakened and is Not Aware
Anxiety Lethargy Locked-In State	Delirium Dementia Psychosis Stupor Vegetative State	Coma Brain Death

Altered States of Consciousness

The principal states of altered consciousness are as follows:

. *Anxiety* and *lethargy* are conditions where arousal and awareness are intact, but there is a change in *attentiveness* (i.e., the degree of awareness).

. A l*ocked-in state* is a condition where arousal and awareness are intact, but there is almost total absence of motor responsiveness. This condition is caused by bilateral injury to the motor pathways in the ventral pons, which disrupts all voluntary movements except up-down ocular movements and eyelid blinking (3).

. *Delirium* and *dementia* are conditions where arousal is intact, but awareness is altered. The change in awareness can be fluctuating (with delirium) or permanent (with dementia).

. *Stupor* is a condition where the subject is difficult to arouse, and is unaware of some or all elements in the environment.

. A *vegetative state* is a condition where there is some degree of arousal (eyes can open), but there is no awareness. Spontaneous movements and motor responses to deep pain can be present, but the movements are purposeless. After one month, this condition is called a *persistent vegetative state* (4).

. *Coma* is the total absence of arousal and awareness (i.e., unarousable unawareness). Like the vegetative state, spontaneous movements and motor responses to deep pain can be present, but the movements are purposeless.

. *Brain death* is similar to coma in that there is a total absence of arousal and awareness. However, brain death differs from coma in two ways: (*a*) it involves loss of all brainstem function, including cranial nerve responses, and spontaneous respirations and (*b*) it is always irreversible.

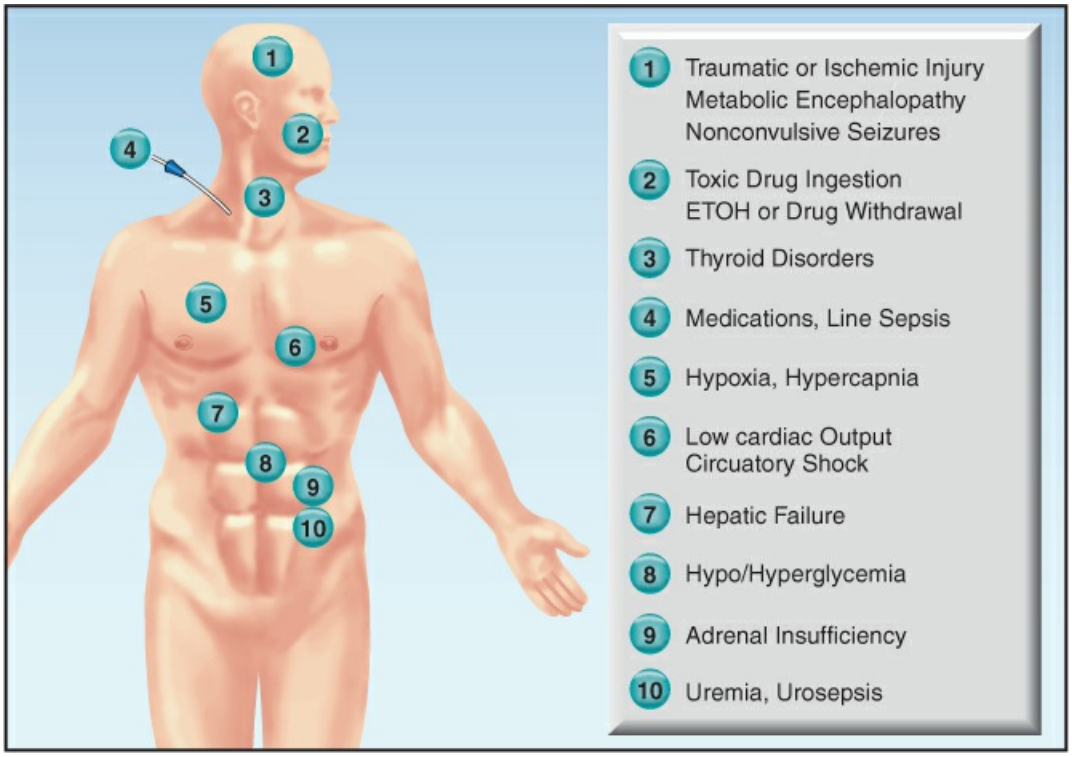


FIGURE 45.1 Common sources of altered consciousness in ICU patients.

Predisposing Conditions

There are an innumerable number of conditions that can alter consciousness, and Figure 45.1 shows a list of the most likely ones in critically ill patients. In a general medical-surgical ICU, the prominent causes of altered consciousness are likely to include the following:

. Sedation during mechanical ventilation.

. Clinical shock syndromes.

. Encephalopathies (ischemic, septic, and metabolic).

. Drug overdoses or withdrawal.

It is worth mentioning that *nonconvulsive seizures* are an often overlooked cause of altered consciousness in ICU patients. (See Chapter 46 for more on this topic.)

DELIRIUM

The delirium described in this section is a manifestation of “brain dysfunction”, which is one part of the multiorgan dysfunction that plagues critically ill patients. The incidence of this type of delirium is about 25–50%, and it is especially common in elderly and ventilator-dependent patients (5). The delirium that is associated with alcohol withdrawal is a separate entity, and is described in a later section.

Clinical Features

The clinical features of delirium are summarized in Figure 45.2 (6,7). As indicated, delirium is a state of inattentiveness (i.e., inability to focus) that has a rapid onset or a rapidly fluctuating course (i.e., changes occur within a 24-hour time period), and is accompanied by either disordered thinking (i.e., incoherent or illogical responses) or an altered level of consciousness (hyperactive or lethargic).

Three types of ICU-related delirium are recognized: (*a*) *hyperactive delirium*, where the patient is restless and agitated, (*b*) *hypoactive delirium*, where the patient is lethargic and somnolent; and (*c*) *mixed delirium*, where there are alternating episodes of hyperactive and hypoactive delirium. *Hypoactive delirium is the most common form* (5), and is often overlooked because of the popular misperception that delirium is a state of severe agitation.

Predisposing Conditions

Any condition that is associated with an encephalopathy can be a source of delirium. The major ones in the ICU are sepsis, liver failure, uremia, and the use of sedative-hypnotic drugs (5).

SEDATION: The use of heavy and prolonged sedation is considered a risk factor for delirium (8), and *benzodiazepines are considered the principal sedatives that promote delirium in the ICU* (9,10). As a result, avoidance of benzodiazepines is considered an important preventive measure for ICU-related delirium (10).

Diagnosis

Validated screening tools are considered essential for the detection of delirium (5), and the *Confusion Assessment Method for the ICU* (CAM-ICU) is probably the most popular of these diagnostic tools (6,7). A summary of the CAM-ICU method is included in Appendix II at the end of the book.

Delirium versus Dementia

Delirium and dementia are distinct mental disorders that can be confused because they have overlapping clinical features (i.e., attention deficits and disordered thinking). However, *delirium has two characteristics that distinguish it from dementia: i.e., the acute onset and fluctuating course*.

Psychosis versus Delirium

Delirium can be difficult to distinguish from psychosis. Over 40% of hospitalized patients with delirium have psychotic symptoms (e.g., visual hallucinations) (11), and delirium has been given the misnomer of “ICU psychosis” (12).

Management

No drug has proven effective in preventing or correcting ICU-related delirium, and drugs are recommended only to restore calm in severely agitated patients (which is not treating the underlying delirium) (5,10). The drugs that can be used for this purpose are included in Table 45.2. Dexmedetomidine is the preferred agent (10), but can produce troublesome bradycardia and hypotension (see Chapter 6). Haloperidol is a popular agent for hyperactive delirium (see

Chapter 6), but has a relatively slow onset of action (which can be a disadvantage in severely agitated patients). Ziprasidone is an atypical antipsychotic agent that can be only be given intramuscularly, but this can be advantageous when intravenous access is problematic in a severely agitated patient (13).

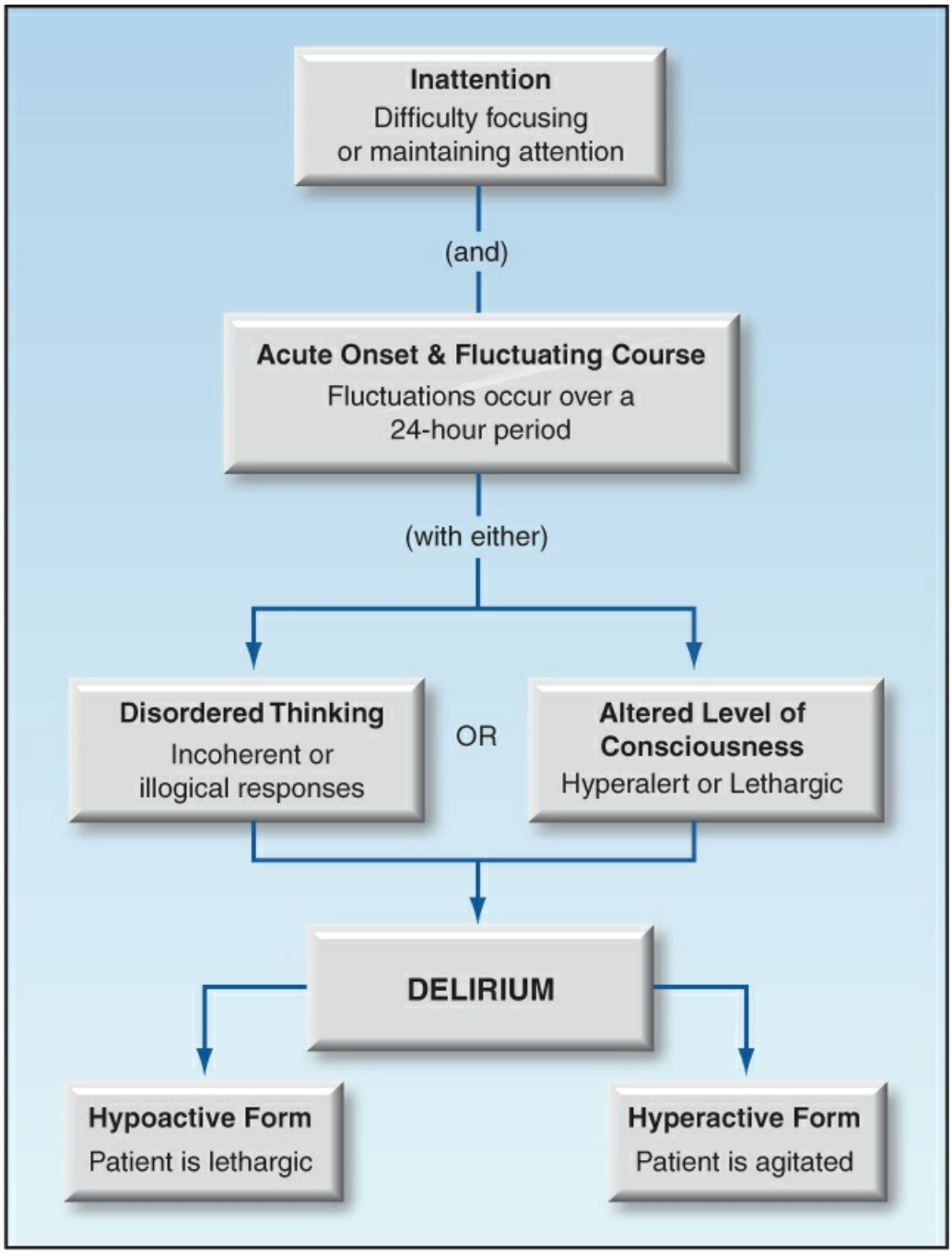


FIGURE 45.2 The clinical features of delirium in critically ill patients.

TABLE 45.2 Drugs for Severe Agitation in ICU-Related Delirium

Drug	Recommendations
Dexmedetomidine	Dosing: Loading dose (optional) is 1 μg/kg IV over 10 min. followed by an infusion of 0.2–1.5 μg/kg/hr. Comment: Can produce bradycardia and hypotension. A withdrawal syndrome (with hyperexcitability) has been reported.
Haloperidol	Dosing: Start with 5 mg IV as a bolus dose. If no effect after 15 min, double the dose (10 mg IV), or switch to another agent. For maintenance dosing, use 25% of the initial effective dose every 6 hrs. Comment: Has a relatively slow onset of action. Not advised if the corrected QT interval is >500 msec.
Ziprasidone	Dosing: 10 mg IM every 2 hrs, or 20 mg IM every 4 hrs, to a total daily dose of 40 mg. Comment: The IM route can be useful if IV access is problematic.

Prevention

The following interventions are recommended for reducing the risk of ICU-related delirium (5,10): (*a*) adequate treatment of pain, (*b*) avoiding deep sedation, when possible, (*c*) promoting sleep-awake cycles, (*d*) encouraging family visitation, (*e*) early ambulation, and (*f*) avoiding benzodiazepines. Unfortunately, these interventions have not been successful in critically ill patients (14).

ALCOHOL WITHDRAWAL

Alcohol (ethanol) is a central nervous system depressant that acts by stimulating the neuronal release of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the mammalian brain (15). Chronic alcohol intake increases the density of GABA receptors in the brain (15), and this certainly contributes to the excitatory state that characterizes the alcohol withdrawal syndrome.

Clinical Features

The clinical features of alcohol withdrawal are shown in Table 45.3 (16). The earliest signs of withdrawal are agitation and tremulousness, which can appear as early as 6 hours after the last drink. This can be followed by generalized seizures. hallucinations (visual, auditory, or tactile), and signs of autonomic hyperactivity (e.g., tachycardia, hypertension). Delirium is a relatively late finding, and is accompanied by increased motor activity. The Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-AR) is the standard method for monitoring the severity of alcohol withdrawal, but it is not recommended for patients with alcohol withdrawal delirium (17). Instead, the CAM-ICU assessment of delirium (which is included in Appendix II) is recommended for alcohol withdrawal delirium (17).

Seizures

Generalized seizures can appear as early as 6–8 hours after the last drink (the risk of seizures peaks at 24 hrs), and they can appear in isolation, without other signs of withdrawal (17). The recommended treatment is lorazepam (2 mg IV push), which prevents recurrent seizures (18).

Phenytoin is not recommended for alcohol-withdrawal seizures (17).

Delirium Tremens

About 5% of patients develop a severe form of alcohol withdrawal known as *delirium tremens* (DTs) (16,17), which appears about 2–3 days after the last drink, and is characterized by hyperactive delirium, hallucinations, and signs of autonomic hyperactivity (e.g., fever, tachycardia, hypertension) that can progress to hemodynamic instability. This condition typically lasts 3–5 days (16), and delirium that persists for longer than 5 days should prompt consideration of another cause of the problem (see later). The hypoactive form of delirium, which is a common presentation of ICU-related delirium, does not occur in alcohol withdrawal delirium.

TABLE 45.3 Clinical Features of Alcohol Withdrawal

Features	Onset after Last Drink	Duration
Early Withdrawal Anxiety, Nausea, Tremulousness	6–8 hrs	1–2 days
Generalized Seizures: One or Two	6–48 hrs	2–3 days
Hallucinations: Visual, Auditory, or Tactile	12–48 hrs	1–2 days
Delirium Tremens: Fever, Tachycardia Hypertension, Delirium (Hyperactive), Autonomic Instability	48–96 hrs	3–5 days

Adapted from Reference 16.

Management

The drugs of choice for treating alcohol withdrawal delirium are the benzodiazepines (17), which mimic the CNS-depressant effects of alcohol by stimulating GABA receptors in the brain (15). Large doses of benzodiazepines (e.g., 30–40 mg of IV lorazepam or 150–200 mg of IV diazepam in 3–4 hours) may be required in severe cases (17).

ICU Management

For patients who require ICU-level care, the benzodiazepines should be given intravenously. *Lorazepam* can be given in a dose of 2–4 mg IV every 5–10 minutes until the desired level of calm is achieved. Thereafter, the dose can be reduced to 2–4 mg IV every few hours as needed. Continuous infusions of high-dose lorazepam (i.e., ≥0.1 mg/kg/hr) should not be continued for longer than 48 hours because of the risk of *propylene glycol toxicity* (see Chapter 6). (The same risk occurs with prolonged infusions of diazepam).

It is important to taper benzodiazepines as soon as possible because they are highly lipid soluble and readily accumulate in the brain with continued use, which can delay awakening and prolong the ICU stay. (See Chapter 6 for more on sedation with benzodiazepines.)

Benzodiazepine Resistance

Benzodiazepine resistance has been described as uncontrolled alcohol withdrawal despite IV lorazepam doses of 30–40 mg or IV diazepam doses of 150–200 mg in the first 3–4 hours of treatment (17). In these cases, the following adjunctive medications have been recommended (17).

. Propofol is a rapidly-acting, GABAergic sedative that is the preferred adjunct to benzodiazepines for patients who are intubated and receiving mechanical ventilation (17). The administration of propofol is described in Chapter 6 (see Table 6.6).

. Phenobarbital is an effective adjunct for benzodiazepines, and can be given in doses of 130–260 mg IV every 15–20 minutes until the desired effect is achieved (19). However, barbiturates should be used cautiously, because they can depress respirations and promote hypotension.

. Dexmedetomidine has been recommended as an adjunct to benzodiazepines (17), using the dosage recommendations in Table 45.2. However, the clinical experience with this drug in severe alcohol withdrawal has not been encouraging (20).

Other Considerations

The following conditions can be mistaken for alcohol withdrawal, and should be considered when there is resistance to benzodiazepines.

Wernicke's Encephalopathy

Patients with alcohol use disorder can experience a sudden deterioration in mental status a few days after admission that is the result of acute Wernicke's encephalopathy (from thiamine deficiency) rather than alcohol withdrawal delirium. This occurs when thiamine stores are borderline depleted on admission, and the glucose load from intravenous fluids and feeding regimens utilizes the remaining thiamine (which is used for glucose metabolism) (21). The presence of nystagmus and oculomotor palsies (e.g., lateral gaze paralysis) can help to identify Wernicke's encephalopathy, but these are infrequent findings.

Patients with alcohol use disorder are typically given thiamine in a dose of 100 mg daily while in the hospital, but this is an insufficient dose for the treatment of Wernicke's encephalopathy. (See Chapter 48 for more on thiamine deficiency.)

Gabapentin Withdrawal

Gabapentin is a GABA analog that is used to treat a variety of disorders, including partial seizures, neuropathic pain, migraine and cluster headaches, psychiatric disorders, and alcohol use disorder. Multiple reports have demonstrated that abrupt discontinuation of gabapentin can result in a hyperactive delirium that is indistinguishable from alcohol withdrawal (22). This usually occurs when the daily dose of gabapentin is 3,000 mg or higher, and the onset can occur from 12 hours to 7 days after the last drug dose. Benzodiazepines are ineffective in controlling the delirium from gabapentin withdrawal, and restarting the gabapentin can have dramatic results (author's experience).

COMA

The patient who is comatose (i.e., unarousable and unaware) is one of the most challenging problems in critical care, as recovery in these patients is never certain.

Etiologies

Coma can be the result of any of the following conditions:

. Diffuse anoxic or ischemic brain injury.

. Supratentorial mass lesion causing transtentorial herniation and brainstem compression.

. Posterior fossa mass lesion causing direct brainstem compression.

. Brainstem stroke.

. Toxic or metabolic encephalopathies (including drug overdose).

. Nonconvulsive status epilepticus.

. Apparent coma (i.e., locked-in state, hysterical reaction).

Bedside Evaluation

The bedside evaluation of coma should include cranial nerve reflexes, spontaneous eye and body movements, and motor reflexes. The following elements of the evaluation deserve mention.

Motor Responses

Spontaneous myoclonus (irregular, jerking movements) can be a nonspecific sign of diffuse cerebral dysfunction, or it can represent seizure activity (myoclonic seizures), while flaccid extremities can indicate diffuse brain injury or injury to the brainstem. A focal motor defect in the extremities (e.g., hemiparesis or asymmetric reflexes) is a sign of a space-occupying lesion or a localized area of brain or spinal cord injury.

RESPONSE TO PAIN: A purposeful response to painful stimulation (e.g., limb withdrawal to pain) is not a feature of the comatose state. Instead, the response to pain is either purposeless or absent. The following responses are determined by a specific area of brain injury:

. With injury to the thalamus, painful stimuli provoke flexion of the upper extremities, which is called *decorticate posturing*.

. With injury to the midbrain and upper pons, the arms and legs extend and pronate in response to pain; this is called *decerebrate posturing*.

. With injury to the lower brainstem, the extremities remain flaccid during painful stimulation.

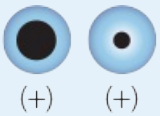
Eye Opening

Spontaneous eye opening is an indication of arousal, and is not consistent with the diagnosis of coma. Spontaneous eye opening can be associated with awareness (i.e., locked-in state) or lack of awareness (i.e., vegetative state).

Examination of Pupils

The conditions that affect pupillary size and light reactivity are shown in Table 45.4 (23–25).

TABLE 45.4 Conditions That Affect Pupillary Size and Reactivity

Pupil Size & Reactivity	Associated Conditions
 (+) (+)	Atropine, anticholinergic toxicity, adrenergic agonists (e.g., dopamine), stimulant drugs (e.g., amphetamines), or nonconvulsive seizures.
 (–) (–)	Diffuse brain injury, hypothermia (<28° C), or brainstem compression from an expanding intracranial mass or intracranial hypertension.
 (–) (+)	Expanding intracranial mass (e.g., uncal herniation), ocular trauma or surgery, or focal seizure.
 (+) (+)	Toxic/metabolic encephalopathy, sedative overdose, or neuromuscular blockade.
 (–) (–)	Acute liver failure, postanoxic encephalopathy, or brain death.
 (+) (+)	Horner's Syndrome
 (+/–) (+/–)	Opiate overdose, toxic/metabolic encephalopathy, hypercapnia, or pontine injury.

(+) and (-) indicate a reactive and nonreactive pupil, respectively. From References 23–25.

Pupillary findings can be summarized as follows:

. Dilated, reactive pupils can be the result of drugs (anticholinergics, CNS stimulants, or adrenergic agonists) or nonconvulsive seizures. Dilated, unreactive pupils can be the result of diffuse brain injury, brainstem compression from an expanding intracranial mass, or increased intracranial pressure.

. A unilateral, dilated and fixed pupil can be the result of ocular trauma or recent ocular surgery, or can be evidence of third cranial nerve dysfunction from an expanding intracranial mass.

. Mid-position, reactive pupils can be the result of a metabolic encephalopathy, a sedative overdose, or neuromuscular blocking drugs, while mid-position, unreactive pupils can be a sign of acute liver failure, postanoxic encephalopathy, or brain death.

. Small, reactive pupils can be the result of a metabolic encephalopathy, while pinpoint pupils can be the result of opioid overdose (pupils reactive) or damage in the pons (pupils unreactive).

Ocular Motility

Spontaneous eye movements (conjugate or disconjugate) are a nonspecific sign of a toxic or metabolic encephalopathy (24), while a fixed gaze preference (one or both eyes) is highly suggestive of a mass lesion or seizure activity.

Ocular Reflexes

The ocular reflexes are used to evaluate the functional integrity of the lower brainstem (24). These reflexes are illustrated in Figure 45.3.

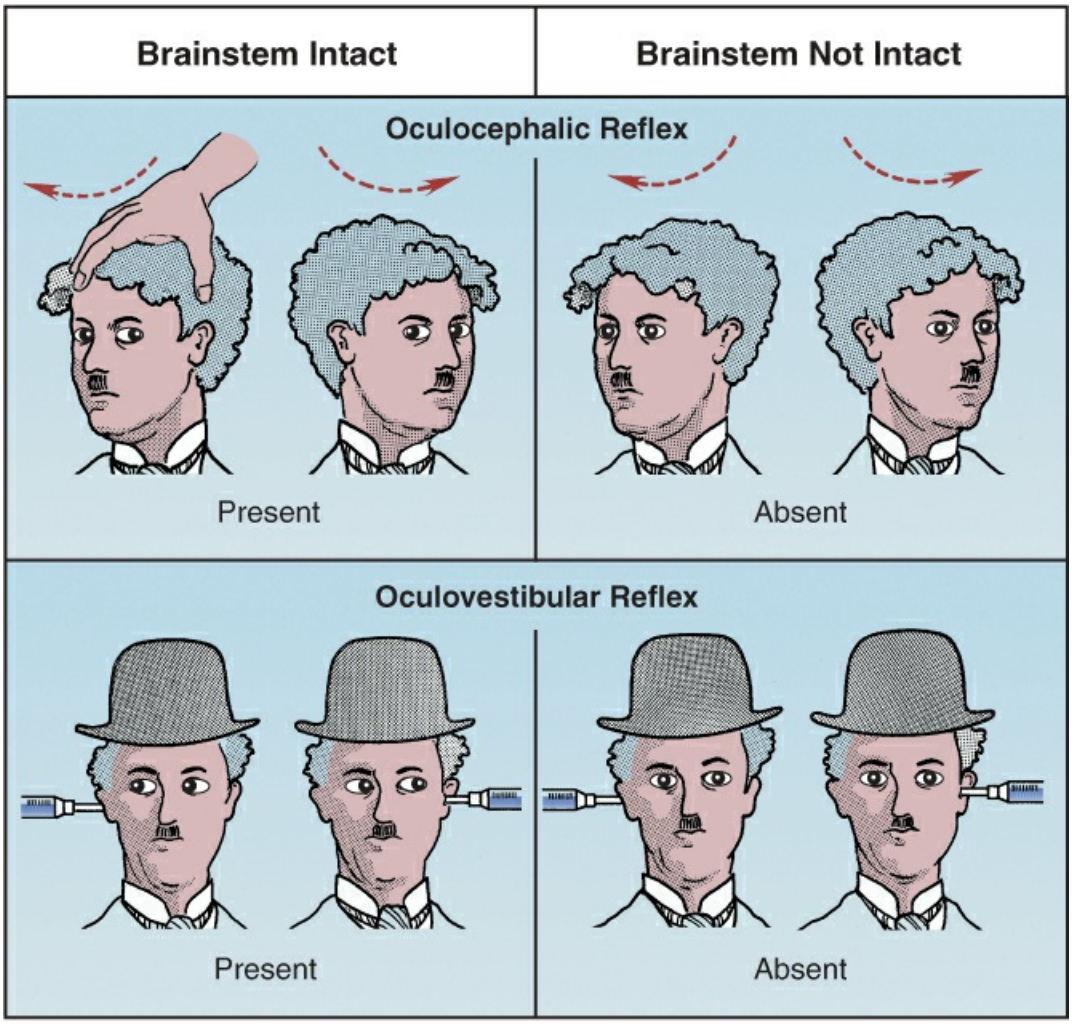


FIGURE 45.3 The ocular reflexes in the evaluation of coma.

OCULOCEPHALIC REFLEX: The oculocephalic reflex is assessed by briskly rotating the head from side-to-side. When the cerebral hemispheres are impaired but the lower brainstem is intact, the eyes will deviate away from the direction of rotation and maintain a forward field of view. When the lower brainstem is damaged (or the patient is awake), the eyes will follow the direction of head rotation. The oculocephalic reflex should *not* be attempted in patients with an unstable cervical spine.

OCULOVESTIBULAR REFLEX: The oculovestibular reflex is performed by injecting 50 mL of cold saline in the external auditory canal of each ear (using a 50 mL syringe and a 2-inch soft plastic angiocatheter). Before the test is performed, check to make sure that the tympanic membrane is intact and that nothing is obstructing the ear canal. When brainstem function is intact, both eyes will deviate slowly towards the irrigated ear. This conjugate eye movement is lost when the lower brainstem is damaged. After the test is performed on one side, wait 5 minutes before testing the opposite side.

The Glascow Coma Score

The Glasgow Coma Scale, which is shown in Table 45.5, was introduced to evaluate the severity of traumatic brain injuries (26,27), but has since been adopted for use in nontraumatic brain injuries (28). The Scale consists of three components: 1) eye opening, 2) verbal communication, and 3) motor response to verbal or noxious stimulation. The *Glasgow Coma Score* (GCS) is the sum of the three components. A minimum score of 3 indicates total absence of awareness and responsiveness, while a maximum score of 15 is normal.

TABLE 45.5 The Glasgow Coma Scale and Score

	Points	
Eye Opening:		
Spontaneous	4	
To speech	3	
To pain	2	
None	1	☐ Points
Verbal Communication:		
Oriented	5	
Confused conversation	4	
Inappropriate but recognizable words	3	
Incomprehensible sounds	2	
None	1	☐ Points
Motor Response:		
Obeys commands	6	
Localizes to pain	5	
Withdraws to pain	4	
Abnormal flexion (decorticate response)	3	
Abnormal extension (decerebrate response)	2	
None	1	☐ Points
Glasgow Coma Score (Total of 3 Scales)*		☐ Points

*Worst score is 3 points, and best score is 15 points. With endotracheal intubation, the highest score is 11.

Interpretations

The GCS is not reliable in patients who are paralyzed, heavily sedated, or hypotensive.

Otherwise, the GCS (best score) can be used as follows:

. To define coma (GCS ≤8).

. To stratify the severity of head injury (mild: GCS = 13–15, moderate: GCS = 9–12, severe: GCS ≤8) (26,27).

. To identify candidates for intubation; i.e., airway protective reflexes are typically defective at a GCS ≤8, which is used as an indication for endotracheal intubation.

. As a prognostic marker; e.g., in the initial evaluation of nontraumatic coma, patients with a GCS ≤6 are seven-times more likely to awaken than patients with a GCS ≤5 (27).

INTUBATED PATIENTS: One of the major shortcomings of the Glascow Coma Scale is the inability of evaluate verbal responses in intubated patients. These patients are assigned a verbal "pseudoscore" of 1 (for a maximum GCS of 11).

BRAIN DEATH

The Uniform Determination of Death Act states that "An individual who has sustained either (*a*) irreversible cessation of circulatory and respiratory functions, or (*b*) irreversible cessation of all functions of the entire brain, including the brainstem, is dead" (29). The evaluation of these requirements is the purpose of the brain death determination.

Brain death is not a common consequence of the nontraumatic coma that is typically encountered in the ICU. It is most often the result of traumatic brain injury or intracerebral hemorrhage, where increases in intracranial pressure are sufficient to cause complete cessation of cerebral blood flow (30). Suspicion of brain death is often prompted by the absence of pupillary light reflexes, or the lack of spontaneous breathing efforts during mechanical ventilation.

Prerequisite Conditions

A checklist for the brain death determination in adults is shown in Table 45.6 (30–32). This checklist begins with conditions that must be satisfied before the brain death determination is performed. The following are some points of interest about the prerequisite conditions.

. Although a systolic pressure ≥100 mm Hg is included as one of the conditions, the mean arterial pressure is the more important physiological pressure, and should be measured if an arterial catheter is in place. Note that the required mean arterial pressure (≥75 mm Hg) is higher than usual target for treating hypotension (≥65 mm Hg). This will help to counteract the effect of increased intracranial pressure to impede cerebral perfusion.

. The absence of effects from CNS-suppressant drugs can be difficult to determine if sedative drugs were used recently. When blood levels of a sedating drug are not available, waiting 5 half-lives since the last dose is recommended to ensure drug clearance from the bloodstream (although this does not guarantee clearance from the brain) (31).

. If targeted temperature management was used with a target below 36° C, then a body temperature of >36° C should be maintained for at least 24 hours before the brain death determination (31).

When the prerequisite conditions are satisfied, the brain death determination can begin. This includes two assessments that are separated by at least 12 hours. One examiner is considered sufficient (in adults) if the examiner is experienced in the task.

TABLE 45.6 Checklist for Brain Death Determination in Adults

Instructions: The patient can be declared legally dead if Steps 1–4 are cofirmed, or there is a positive confirmatory test.	**Check (√) Item if Confirmed**	
Step 1: Prerequisites: All of the following conditions should be satisfied prior to the brain death determination. • At least 48 hrs has elapsed since the brain injury. • The systolic pressure is ≥100 mm Hg, or the mean arterial pressure is ≥75 mm Hg. • The body temperature is >36° C (96.8° F). • There is no hypothyroidism or hypoglycemia. • There are no CNS-depressant drug effects.	☐	
Step 2: Establish the Cause of Coma: The cause of coma is known, and is sufficient to cause irreversible brain death.	☐	
Step 3: Absence of Brain, and Brainstem, Function: Two examinations are required, separated by at least 12 hrs. A single examiner is sufficient, if adequately trained. A. The patient is comatose (unaware and unresponsive). B. The following brainstem reflexes are absent: • Absent pupillary response to bright light. • Absent corneal reflex. • Absent gag and cough reflexes • Absent oculocephalic reflex • Absent oculovestibular reflexes (bilaterally)	**First Exam** ☐ ☐	**Second Exam** ☐ ☐
Step 4: Absence of Spontaneous Breathing Efforts: There are no spontaneous breathing efforts when the arterial PCO_2 is >60 mm Hg, and >20 mm Hg above the patient's baseline level.	☐	
Step 5: Confirmatory Tests: Confirmatory tests are indicated only when Steps 1–4 cannot be completed or unequivocally interpreted. Acceptable tests are (1) transcranial Doppler ultrasound, (2) radionuclide cerebral blood flow scan, or (3) 4-vessel catheter angiography.		

Adapted from the clinical practice guideline in Reference 31.

Brainstem Reflexes

The brain death determination begins with an evaluation of the reflexes that require a functioning brainstem: i.e., the corneal and pupillary light reflexes, the oculocephalic and oculovestibular reflexes, and the gag and cough reflexes. All these reflexes must be absent to proceed with the evaluation.

The Apnea Test

The most convincing evidence of brain death is the absence of spontaneous breathing efforts in the face of an increased arterial PCO_2 ($PaCO_2$). (*Note:* CO_2 is a potent respiratory stimulant: i.e.,

an increase in $PaCO_2$ of only 1 mm Hg will increase the minute ventilation by 2 L/min (32).) The evaluation of spontaneous breathing efforts is called the *apnea test*, and it proceeds as follows:

. Prior to the test, the patient is preoxygenated with 100% O_2, and an arterial blood gas is obtained to establish the baseline $PaCO_2$.

. The patient is then separated from the ventilator and oxygen is insufflated into the endotracheal tube (apneic oxygenation) to help prevent O_2 desaturation during the apneic period.

. The goal of the apnea test is to allow the $PaCO_2$ to rise 20 mm Hg above baseline. The $PaCO_2$ rises about 3 mm Hg per minute during apnea at normal body temperatures (33), so an apnea period of 6–7 minutes should be sufficient for reaching the target $PaCO_2$. A repeat arterial blood gas is obtained at the end of the apnea period, and the patient is placed back on the ventilator.

. If apnea persists despite a rise in $PaCO_2$ ≥20 mm Hg, the test confirms the diagnosis of brain death.

. If the second apnea test confirms the diagnosis of brain death, *the time of death is the time that the second blood gas results became available* (31). However, patients are often kept on mechanical ventilation for a short period of time after this, to allow family members to have a final visit with the patient.

The apnea test is risky, because O_2 desaturation, hypotension, and serious cardiac arrhythmias can appear during the apnea period (34). If the apnea test cannot be completed, confirmatory testing is required to establish the diagnosis of brain death.

Lazarus' Sign

Brain-dead patients can exhibit brief, spontaneous movements of the head, torso, or upper extremities (*Lazarus' Sign*), especially after they are removed from the ventilator (35). These movements are the result of neuronal discharges in the cervical spinal cord, possibly in response to hypoxemia, and they can be a source of angst when they appear after the patient has been pronounced brain dead and is removed from the ventilator.

Confirmatory Tests

The acceptable confirmatory tests are included in Table 45.6. Confirmatory tests that are not considered acceptable include electroencephalography (EEG), auditory and somatosensory evoked potentials, computed tomographic angiography, and magnetic resonance angiography (31).

A FINAL WORD

Family Care

In the care of the patient with persistent coma or a persistent vegetative state, spending time with the patient's family and/or close acquaintances to explain what is happening (and what is likely

to happen), is as vital as patient care. These people will look to you for guidance in making end-of-life decisions, and avoiding *the conspiracy of silence* (36) is one of the greatest services you can perform as a physician.

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Chapter 46

Disorders of Movement

When we contemplate this life, we see motion as its principal characteristic, and when we take a farther view, we see that this motion must necessarily waste the machine in which it resides.

John Young (*a*)

This chapter describes three movement disorders that you are likely to encounter in the ICU: (*a*) involuntary movements (i.e., seizures), (*b*) weak or ineffective movements (i.e., neuromuscular weakness), and (*c*) no movements (i.e., drug-induced paralysis). These conditions are aberrations of the motion described by John Young in the introductory quote, but they retain the ability to "waste" the human machine.

SEIZURES

The risk of seizures in critically ill patients is determined primarily by the presence and type of brain injury, rather than the general condition of the patient (e.g., severity of shock). The conditions that typically produce new-onset seizures are listed in Table 46.1, along with the reported frequency of seizures (1–3). Also included in Table 46.1 is the frequency of troublesome seizures that either persist or recur before the patient recovers from the prior one. This condition is known as *status epilepticus*, and it is the principal focus of this section.

TABLE 46.1 Reported Occurrence Rates of Seizures

Condition	Seizures	Status Epilepticus
Traumatic Brain Injury	20–50%	15–25%
Ischemic Brain Injury	40%	30%
Encephalitis*	35–45%	20%
Intracerebral Hemorrhage	20–30%	10–20%
Subarachnoid Hemorrhage	10–20%	15%

No Neurologic Illness	4–15%	<1%
Acute Ischemic Stroke†	2–5%	—

*Includes infectious and autoimmune encephalitis.
† Includes only the early period (one week) after acute stroke.
Data from References 1–3.

Types of Seizures

Seizures are classified by the presence or absence of abnormal movements (convulsive versus nonconvulsive seizures), the type of abnormal movement (e.g., tonic–clonic, myoclonic), and the extent of involvement (generalized versus focal seizures).

Abnormal Movements

The movements associated with seizures can be *tonic* (caused by sustained muscle contraction), *clonic* (rhythmic movements with a regular amplitude and frequency) or *myoclonic* (irregular, jerky movements that vary in amplitude and frequency). The abnormal movements can also be familiar but repetitive (e.g., chewing or lip smacking); these are called *automatisms*. Of interest, myoclonus is not universally regarded as a seizure because it is not associated with rhythmic discharges on the EEG (4).

Generalized vs. Focal Seizures

Generalized seizures arise from synchronous, rhythmic electrical discharges that involve most of the cerebral cortex, and they are always associated with loss of consciousness. However, they are not always associated with abnormal (convulsive) movements. Focal seizures arise from discrete areas of the brain, and may or may not be accompanied by loss of consciousness. However, focal seizures often progress to generalized seizures (1).

Partial Complex Seizures

Partial complex seizures are nonconvulsive seizures that produce behavioral changes. The typical manifestation is a patient who is awake but not aware of the surroundings (similar to absence seizures). These are often preceded by an *aura* (e.g., a particular smell), and can be accompanied by automatisms.

Status Epilepticus

Status epilepticus (SE) in adults is traditionally defined as ≥*5 minutes of continuous seizure activity, or two or more discrete seizures without an intervening period of consciousness* (5). There are about 20 different types of SE (5), but the ones most likely to be seen in the ICU are (*a*) generalized convulsive and nonconvulsive SE, (*b*) myoclonic SE, and (*c*) focal motor SE (with and without loss of consciousness). Nonconvulsive SE is of particular interest as a source of impaired consciousness.

TABLE 46.2 Clinical Manifestations of Nonconvulsive Status Epilepticus

Impaired Consciousness	Others

Confusion (49%) Coma (22%) Lethargy (21%)	Speech Disturbances (15%) Myoclonus (13%) Bizarre Behavior (11%) Agitation or Delirium (8%) Hallucinations (6%)

Frequency of occurrence in parentheses. From Reference 6.

Nonconvulsive SE

Nonconvulsive SE is an elusive diagnosis because the clinical manifestations are varied and atypical for seizures. This is demonstrated in Table 46.2, which shows the clinical manifestations in 105 reported cases of nonconvulsive SE (6). Impaired consciousness (i.e., confusion, coma, or lethargy) was the most common manifestation, and was present in about 80% of cases. The remaining manifestations included speech disturbances, bizarre behavior, agitation, delirium, and hallucinations.

The importance of nonconvulsive seizures as a cause of impaired consciousness is demonstrated by the following observations:

. In ICU patients with impaired consciousness, nonconvulsive seizures have been detected in 16% of the patients when continuous EEG monitoring is used (usually for 1–2 days) (7), and in 4–8% of the patients when intermittent EEG recordings are used (7,8).

. Nonconvulsive seizures have been detected in 37% of the EEGs obtained for the evaluation of impaired consciousness (9).

Observations like these emphasize the need to consider nonconvulsive seizures in any ICU patient with impaired consciousness, and to use continuous EEG monitoring when available.

Treatment

The pharmacotherapy of SE is divided into three steps, and the drugs involved in each of these steps are presented in Tables 46.3 and 46.4. Seizures that continue uninterrupted for longer than 30 minutes can result in permanent neuronal injury (5), emphasizing the need for prompt suppression of SE. *Note:* The treatment of SE presented here is primarily intended for generalized convulsive SE (10), but it is also used (with less success) for nonconvulsive SE.

Step 1: Benzodiazepines

Benzodiazepines are the first-line drugs of choice for the rapid termination of generalized SE (10). *Intravenous lorazepam is the preferred agent* (10,11), *and intramuscular midazolam is effective when IV access is problematic* (12). Intravenous diazepam is also effective, but is not favored because of rapid washout from the brain, which increases the risk of seizure recurrence (1).

LORAZEPAM: Intravenous lorazepam can terminate generalized convulsive SE in about two minutes, and the effect lasts for 6–12 hours (11). The recommended dosage is 0.05–0.1 mg/kg (or 4 mg) IV over 2 minutes, which can be repeated once if needed.

MIDAZOLAM: Midazolam can be given by IV or intramuscular (IM) injection, and the

recommended dose is 0.15 mg/kg, or 10 mg (10). IM midazolam is as effective as IV lorazepam (12), and the IM route is advantageous when IV access is problematic (e.g., in the prehospital setting).

Step 2: Anticonvulsants

About one-third of cases of generalized SE do not respond to benzodiazepines (13), and the next step is the administration of a nonsedating anticonvulsant: i.e., levetiracetam, fosphenytoin, or valproic acid. All are equivalent in terminating SE (which occurs in about half of the cases) (14), but *levetiracetam is often favored because it has fewer side effects.*

LEVETIRACETAM (KEPPRA®): The recommended dose of levetiracetam in generalized SE is 60 mg/kg IV, infused over 5–15 minutes, with a maximum single dose of 4,500 mg (10). If necessary, the drug can be continued at a dose of 1,000 mg IV every 12 hours, and serum drug levels can be used to adjust dosage. There is no risk of hypotension or respiratory depression, and no drug interactions.

FOSPHENYTOIN: Fosphenytoin is a water-soluble prodrug that produces less cardiac depression and hypotension than phenytoin because it does not contain the solvent propylene glycol. (See Chapter 6 for a description of propylene glycol toxicity.) As a result, fosphenytoin can be infused three times faster than phenytoin (at 150 mg/min) (15). The dosing is the same as phenytoin, but is expressed as phenytoin equivalents (PE), as shown in Table 46.3. If the drug is effective, maintenance therapy is started at 100 mg PE IV every 8 hours, and serum levels are monitored to guide dosing.

The parent drug, phenytoin, has several undesirable features, including CNS toxicity (lethargy, confusion, ataxia) and multiple drug interactions (due to its metabolism by the cytochrome P450 system in the liver). The conversion of fosphenytoin to phenytoin is increased in liver failure, and careful monitoring of serum phenytoin levels is advised in patients with hepatic insufficiency.

TABLE 46.3 Drugs Regimens for Status Epilepticus

Drug	Recommendations
Step 1: Benzodiazepines	
Lorazepam	Dosing: 0.1 mg/kg (or 4 mg) IV over 2 min. Repeat in 5 min, if needed. Comment: The preferred drug regimen for terminating SE. Onset of action is <2 min, and effect lasts 6–12 hrs.
Midazolam	Dosing: 0.15 mg/kg (or 10 mg) IV, or by intramuscular (IM) injection. Comment: IM midazolam is as effective as IV lorazepam, and the IM route is advantageous when IV access is problematic (e.g., in the field).
Step 2: Anticonvulsants	
Levetiracetam	Dosing: 60 mg/kg IV over 5–10 min. Max single dose is 4,500 mg. Comment: Is often preferred to the other anticonvulsants because it has few side effects.

Fosphenytoin	Dosing: 20 mg PE/kg IV at ≤150 mg/min. Max single dose is 1,500 mg PE. Comment: A water soluble prodrug with less risk of hypotension than phenytoin because it does not contain the solvent propylene glycol.
Valproic Acid	Dosing: 40 mg/kg IV over 5–10 min. Max single dose is 3,000 mg. Comment: As effective as the other anticonvulsants. Only side effect of con-cern is hyperammonemia, which creates a risk of encephalopathy.

Drug dosing from the guidelines in Reference 10. PE = phenytoin equivalents.

VALPROIC ACID: Valproic acid is equivalent to the other anticonvulsants for terminating SE (14) (see Table 46.3 for the recommended dose), and has relatively few side effects (16). However, it is far less popular than the other anticonvulsants (author's observation). One side effect that has gained some attention is a 40% risk of hyperammonemia (17), which can produce an encephalopathy.

Step 3: Refractory Status Epilepticus

About 10–15% of cases of generalized SE are refractory to step 1 and 2 drugs, and the treatment for these cases is anesthetic doses of one of the drugs in Table 46.4. There is no evidence that one drug regimen is superior to the others, and selection is often based on familiarity. Patients should be intubated and on mechanical ventilation prior to starting these drugs, as they all depress ventilation in the recommended doses. Continuous EEG monitoring is also advised, and at this point, consultation with a critical care neurologist or epileptologist is the best option. (*Note:* Drugs other than those in Table 46.4 can be used for refractory SE, including thiopental, phenobarbital, and ketamine. The dosing regimens for these drugs are available in Reference 1.)

Outcomes

The in-hospital mortality rates are as high as 21% for generalized convulsive SE, about 50% for generalized nonconvulsive SE, and as high as 61% for refractory SE (7).

TABLE 46.4 Drug Regimens for Refractory Status Epilepticus

Drug	Dosing Regimens
Propofol	Start with an IV bolus dose of 1–2 mg/kg, and begin infusion at 1 mg/kg/hr. Titrate upward as needed to max dose rate of 15 mg/kg/hr (or 5 mg/kg/hr if infusion longer than 48 hrs).
Midazolam	Load with 0.2 mg/kg IV, then infuse at 0.2 mg/kg/hr, and titrate upward as needed to a max. dose rate of 4 mg/kg/hr.
Pentobarbital	Load with 5–15 mg/kg IV over one hr, then begin infusion at 1 mg/kg/hr. Titrate upward, if needed, to a max. dose rate of 5 mg/kg/hr.

Dosing regimens from Reference 1.

NEUROMUSCULAR WEAKNESS SYNDROMES

The following is a description of neuromuscular weakness syndromes that you may encounter in the ICU.

Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disease produced by antibody-mediated destruction of acetylcholine receptors on the postsynaptic side of neuromuscular junctions (18). Skeletal muscles are the only target of this illness.

Predisposing Conditions

MG can be triggered by major surgery or a concurrent illness. Thymomas are responsible for 10% of cases of MG (18). MG can also be aggravated by major surgery, physiological stress, and drugs that can impair neuromuscular transmission. The drugs that can aggravate MG are listed in Table 46.5. These drugs should not be used in patients with MG. However, note that high-dose corticosteroids are listed as aggravating MG, which is concerning because high-dose steroids are used to *treat* MG. (For more on this, see Reference 20.)

TABLE 46.5 Drugs that can Exacerbate Myasthenia Gravis

1. *Antibiotics:* aminoglycosides, fluoroquinolones, macrolides, penicillins
2. *Cardiovascular Drugs:* β-blockers, calcium channel blockers, class Ia antiarrhythmics (procainamide, quinidine, disopyramide)
3. *Neuromuscular Blockers:* both depolarizing and non-depolarizing agents
4. *Others:* high-dose steroids*, inhalational anesthetics, magnesium, lithium

*High-dose steroids are also used to treat myasthenia gravis. The list of drugs is from References 19 and 20.

Clinical Features

Skeletal muscle weakness is the sole manifestation of MG, and the weakness has the following characteristics:

. The eye muscles (i.e., eyelid and oculomotor muscles) are always involved, and the earliest signs of MG are diplopia and ptosis. Symmetrical limb weakness usually follows, but in 15% of cases, the weakness is confined to the eye muscles (18).

. The muscle weakness typically worsens with muscle activity, and improves with rest.

. The deficit is purely motor, and deep tendon reflexes are preserved.

. Progressive disease leads to weakness of the diaphragm and chest wall muscles, and rapid progression to respiratory failure, called *myasthenic crisis,* occurs in 15–20% of patients (21).

Diagnosis

The diagnosis of MG is suggested by the pattern of muscle weakness, with ptosis as a dominant feature. Confirmatory diagnostic tests include the ice test, and serum antibody levels.

ICE TEST: The ice test is based on the premise that cooling can improve neuromuscular transmission in MG. The test is performed on an eyelid with ptosis, and the distance between the upper and lower eyelids (the edges of the palpebral fissure) is measured. An ice pack (or plastic glove filled with ice) is then placed on the eyelid (with the eyes closed) for 2 minutes. An increase of 2 mm in the distance between the upper and lower eyelids is a positive test, and helps

confirm the diagnosis of MG. This is illustrated in Figure 46.1. A positive ice test has a sensitivity and specificity of 80% for the diagnosis of MG (22).

AUTOANTIBODY ASSAYS: The presence of acetylcholine (Ach) receptor antibodies in the serum confirms the diagnosis of MG. About 10–15% of patients with MG will not have Ach antibodies in the blood (18), and for these cases, a muscle-specific kinase (MuSK) antibody should be assayed. This antibody is present in about 40% of MG patients who have no detectable Ach antibodies (23).

Management in the ICU

Most cases of MG that are severe enough to warrant ICU-level care have respiratory muscle weakness, with some degree of respiratory insufficiency. The principal concern in these patients is determining when intubation is necessary.

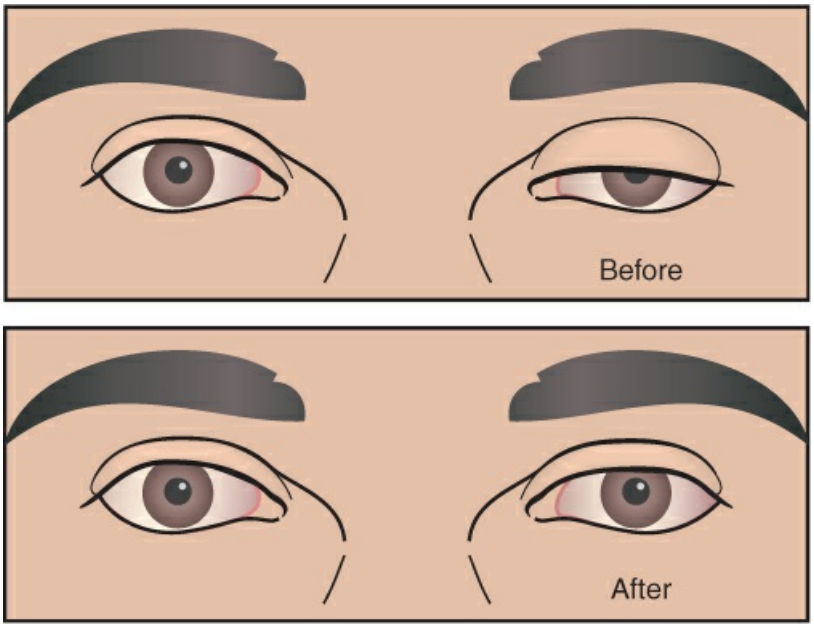

FIGURE 46.1 Illustration of a positive ice test for the diagnosis of myasthenia gravis. An icepack is applied to the eyelid with ptosis for 2 minutes, and this results in an increase in the distance between the upper and lower eyelids.

INTUBATION: The deterioration in ventilatory status can be very rapid in MG, so intubation should not be delayed until the patient is *in extremis*. Measurements of vital capacity and maximum inspiratory pressure (i.e., the negative pressure generated by a maximum inspiratory effort against a closed valve) can be used to guide decisions about intubation. *A vital capacity of ≤15 mL/kg (or <1 liter), and a maximum inspiratory pressure of –20 cm H_2O (normal being >–100 cm H_2O) should prompt serious consideration of intubation and mechanical ventilation* (21). Noninvasive ventilation with BIPAP (described in Chapter 26) should only be considered if an improvement in respiratory status is expected in the next few days (which is usually not the case).

TREATMENT FOR MYASTHENIC CRISIS: There are two options for treating severe MG with

respiratory failure (i.e., myasthenic crisis) (21):

. *Intravenous immunoglobulin*, or IVIG, (to neutralize the pathologic antibodies) in a dose of 2 grams per kilogram body weight, administered over 2–5 days.
. *Plasmapheresis* (to remove the pathologic antibodies from the bloodstream), which typically involves 5 sessions over 7–10 days, with each session exchanging 1.0 to 1.5 plasma volumes.

Both treatments are equally effective, and will produce a favorable response in about 70% of patients (21). However, plasmapheresis is favored because it produces a faster response: i.e., the response to IVIG is not evident for 4–5 days, while the response to plasmapheresis may be apparent after the second session (21).

PYRIDOSTIGMINE: Pyridostigmine (Mestinon®) is an acetylcholinesterase inhibitor that is typically given to patients with mild-to-moderate MG (24,25). However, the drug is not used when MG progresses to respiratory failure, because one of the side effects is to increase respiratory secretions (cholinergic effect).

CORTICOSTEROIDS: High-dose methylprednisolone (2 grams daily for two days) has been used to treat myasthenic crisis, with some evidence of success (26). However, this treatment is debated because of reports that high-dose corticosteroids can also aggravate MG, as mentioned earlier. It certainly seems wise to withhold this treatment in patients who are responding satisfactorily to IVIG or plasmapheresis.

OTHER CONSIDERATIONS:

. Prophylaxis for venous thromboembolism (e.g., enoxaparin 40 mg daily) is considered particularly important in diseases with neuromuscular weakness, because of limited mobility.
. Patients with bulbar weakness can also have difficulty swallowing, which creates a risk of aspiration of saliva into the airways. Patients who are not intubated should therefore have a swallowing evaluation to assess the risk of aspiration.
. Patient's with new-onset MG should have a contrast-enhanced CT of the chest to search for a thymoma. If one is present, a thymectomy may be appropriate to reduce the need for immunotherapy. This decision, and the use of immunotherapy for long-term management of MG, will be the purview of a neurologist.

Outcomes

About 95% of patients who are hospitalized with MG will survive the hospitalization (21), but few will recover completely (18).

Guillain–Barré Syndrome

The Guillain–Barré syndrome (GBS) is an *inflammatory demyelinating polyneuropathy* that often follows an acute infectious illness (by 1 to 3 weeks). Infectious organisms that predispose to GBS include *Campylobacter jejuni*, Zika virus, and SARS coronavirus-2 (27). An immune mechanism is suspected, and *molecular mimicry* has been implicated (27). (*Note:* In molecular

mimicry, antibodies to a component of pathogens cross-react with a component of peripheral nerves.)

Clinical Features

The clinical presentation of GBS is characterized by paresthesias and symmetrical limb weakness (upper and lower limbs) that progresses over a few days to a few weeks. Progression to respiratory failure occurs in 25% of cases (28), and autonomic instability is a feature in advanced cases (29). The condition resolves spontaneously in about 80% of cases, but residual neurological deficits are common (28).

The features that distinguish GBS from myasthenia gravis are shown in Table 46.6. There is no oculomotor weakness in GBS, although there is a GBS variant known as the *Miller Fisher syndrome* that presents with ophthalmoplegia and ataxia (30). Another characteristic feature of GBS is the deep tendon reflexes, which are diminished or absent.

Diagnosis

The diagnosis of GBS is based on the clinical presentation (symmetrical limb weakness presenting within a few weeks of an infection), and nerve conduction studies that show a decrease in nerve conduction velocity. Lumbar puncture is often performed to rule out other conditions, and the cerebrospinal fluid shows elevated protein levels in patients with GBS (31).

TABLE 46.6 Features that Distinguish Guillain–Barré Syndrome from Myasthenia Gravis

Feature	Guillain–Barré Syndrome	Myasthenia Gravis
Oculomotor Weakness	No	Yes
Fatigable Weakness	No	Yes
Deep Tendon Reflexes	Diminished	Intact
Autonomic Instability	Yes	No
Nerve Conduction	Slowed	Normal
Cerebrospinal Fluid	↑ Protein	Normal

Treatment

Patients with GBS who require ICU-level care are managed in a very similar fashion to the management described for myasthenia gravis.

. Respiratory deterioration can be rapid, and monitoring the vital capacity and negative inspiratory pressure can help in timely intubation, before the patient is *in extremis*.

. Patients who are unable to walk unaided, or have respiratory failure, should be treated with *intravenous immunoglobulin or plasmapheresis* (31), using the same regimens described earlier for myasthenia gravis. Both treatments are considered equivalent, and no preference is given in the most recent guidelines on GBS (31).

PAIN: Pain can be prominent in the acute and resolving stages of GBS, and is considered to be neuropathic rather than nociceptive pain. The recommendation from the guidelines on GBS is *gabapentin* (Neurontin®) in a dose of 300 mg three times daily (31). However, opioids should also be considered for more immediate pain relief, since they can be effective for relieving neuropathic pain (32).

Outcomes

In the United States, about 97% of patients who are hospitalized for GBS will survive the hospital stay (33), but 10–15% of these patients will be severely disabled (34).

Critical Illness Neuromyopathy

The disorders known as *critical illness polyneuropathy* (CIP) and *critical illness myopathy* (CIM) are secondary disorders, and typically occur in patients with severe systemic inflammatory diseases (35–37). These disorders often co-exist in the same patient, and become apparent when patients fail to wean from mechanical ventilation.

Pathogenesis

. CIP is a diffuse sensory and motor axonal neuropathy that is particularly prevalent in patients with severe sepsis and septic shock (37). It affects both limb and truncal muscles, and is considered the most common peripheral neuropathy in critically ill patients (38).

. CIM is a diffuse inflammatory myopathy that involves both limb and truncal muscles (39). Predisposing conditions include severe sepsis and septic shock, immobility (e.g., by neuromuscular paralysis), and hyperglycemia (36,37). An acute myopathy that resembles CIM has also been reported in ventilator-dependent asthmatic patients who were paralyzed and treated with high dose steroids (40).

The common denominator in both CIP and CIM is severe or progressive systemic inflammation (36,37), so both conditions could represent inflammatory organ injury. This would then add to the spectrum of inflammatory organ injury described in critically ill patients (see Table 17.1). This topic is revisited in the very last section of the chapter (A FINAL WORD).

Clinical Features

Both CIP and CIM produce a flaccid paralysis in limb and truncal muscles, associated with hyporeflexia or areflexia (36). However as just mentioned, these conditions often go undetected until there is an unexplained failure to remove a patient from mechanical ventilation.

. The diagnosis of CIP is secured by nerve conduction studies, which show slowed conduction in sensory and motor fibers (41).

. The diagnosis of CIM can be confirmed by electromyography (which shows myopathic change) and by muscle biopsy (which shows loss of myosin filaments, and inflammatory infiltration) (39).

Management

There is no treatment for CIP or CIM. Several measures have been proposed to reduce the risk of

these disorders (e.g., early ambulation, improved nutrition), but none have been validated (and none are directed at the inflammatory nature of the disorders).

Outcomes

These conditions can be devastating in ventilator-dependent patients, because they prevent weaning from ventilatory support. Complete recovery is expected in about half the patients (41), but it can takes months to recover.

DRUG-INDUCED PARALYSIS

Neuromuscular blocking agents produce a flaccid paralysis that is used in the following situations: (*a*) to facilitate endotracheal intubation, (*b*) to prevent shivering during induced hypothermia, and (*c*) to promote synchronous mechanical ventilation in patients who are severely agitated (42).

These agents act by binding to acetylcholine (Ach) receptors on the postsynaptic side of neuromuscular junctions. Once bound, there are two different modes of action: (*a*) *depolarizing agents* produce a sustained depolarization of the postsynaptic membrane, and (*b*) *non-depolarizing agents* act by competitive inhibition of Ach binding to the postsynaptic receptors. Both actions effectively block the transmission of electrical impulses from nerve to muscle.

Commonly Used Agents

The comparative features of three commonly used neuromuscular blocking agents are shown in Table 46.7 (43). *Note:* Many experts recommend that ideal body weight be used for dosing of neuromuscular blockers (42).

TABLE 46.7 Properties of Commonly-Used Neuromuscular Blocking Agents

	Succinylcholine	Rocuronium	Cisatracurium
Intubating Dose (IV)	1–1.5 mg/kg	1.0 mg/kg	0.15–0.2 mg/kg
Onset Time	1–1.5 min	1.5–3 min	5–7 min
Clinical Duration	7–12 min	50–70 min	35–50 min
Infusion Dose	—	5–12 µg/kg/min	1–3 µg/kg/min
Cardiovascular Effects	Bradycardia	None	None
Contraindications	Multiple†	None	None
Influence of Renal or Hepatic Dysfunction	None	Prolonged effect with liver failure	None

†Contraindications to succinylcholine include hyperkalemia, malignant hyperthermia, rhabdomyolysis, burns, and immobility from spinal chord injury.

Properties of the neuromuscular blockers from Reference 43.

Succinylcholine

Succinylcholine is the only depolarizing agent available, and has both a rapid onset of action (60–90 seconds) and a rapid recovery time (7–12 minutes). Because of these features, succinylcholine is popular for rapid-sequence endotracheal intubation.

SIDE EFFECTS: Succinylcholine-induced depolarization of skeletal muscle promotes the efflux of K^+ from muscle cells. This can be associated with up to a 0.5 mEq/L rise in the serum K^+ (44), but this effect is without consequence if the baseline serum K^+ is not elevated. However, life-threatening hyperkalemia can occur when succinylcholine is given to patients with hyperkalemia, or to patients with malignant hyperthermia, rhabdomyolysis, burns, or immobility from spinal cord injury. As a result, succinylcholine is contraindicated in these conditions.

Rocuronium

Rocuronium is a non-depolarizing neuromuscular blocker with a rapid onset of action (1.5–3 minutes) and an "intermediate" duration of clinical effect (30–70 min). It has no cardiovascular side effects, and has gradually replaced vecuronium, a related drug with a more delayed onset of action. Rocuronium has a prolonged effect in patients with hepatic dysfunction (43), but the extent of the prolongation has not been adequately studied.

INTUBATION: Because of the rapid onset of action, rocuronium can be used for endotracheal intubation when succinylcholine is contraindicated. At a dose of 1.0 mg/kg, rocuronium has a rapid onset that is equivalent to a 1.0 mg/kg dose of succinylcholine (45). The only concern with rocuronium is the prolonged duration of effect (about one hour), which can be problematic if the airway is not secured in a timely fashion. In this situation, rapid reversal of rocuronium with sugammadex (16 mg/kg) is advised. (See later for reversal agents.)

Cisatracurium

Cisatracurium is a non-depolarizing agent with a prolonged onset of action (5–7 min) and an intermediate duration of effect (35–50 min). Unlike a related agent (atracurium), cisatracurium does not cause histamine release, and it has no cardiovascular side effects (43). Blood levels of cisatracurium are not influenced by renal or liver failure, which makes it an appealing neuromuscular blocker for ICU patients.

Monitoring

The standard method of monitoring drug-induced paralysis is to apply a series of four low-frequency (2 Hz) electrical pulses to the ulnar nerve at the forearm, and observe for adduction of the thumb. Total absence of thumb adduction is evidence of excessive block. The desired goal is 1 or 2 perceptible twitches, and the drug infusion is adjusted to achieve that end-point (30).

Reversal Agents

There are two agents that can reverse neuromuscular blockade: *neostigmine* and *sugammadex*.

Neostigmine

Neostigmine blocks the breakdown of Ach (by inhibiting the acetylcholinesterase enzyme), and the subsequent increase in Ach is enough to overcome the competitive blockade by the

nondepolarizing agents. (There are two other "anticholinesterases", edrophonium and pyridostigmine, but neither is used as a reversal agent.)

DOSAGE: The dose of neostigmine needed to reverse neuromuscular paralysis is dependent on several factors, including the neuromuscular blocker, the depth of paralysis, and the anesthetic agent that is used. An intravenous neostigmine dose of 70 μg/kg can reverse a moderate level of paralysis, but the recovery time can vary from 8 to 45 minutes, depending on the other factors just mentioned (43). The dose of neostigmine should never exceed 70 μg/kg because of the risk of parasympathomimetic side effects (43).

Sugammadex

Sugammadex is a reversal agent that binds directly to the aminosteroid class of neuromuscular blockers (i.e., rocuronium, vecuronium, and pancuronium). It binds most tightly to rocuronium, but is equally effective for vecuronium. (The binding to pancuronium is far less extensive.)

DOSAGE: The dose of sugammadex depends on the depth of paralysis. To reverse rocuronium within minutes after it is administered (i.e., after an intubation), the sugammadex dose is 16 mg/kg, and the reversal time is only 2–3 minutes (which is less than the recovery time for succinylcholine) (43). With deep paralysis, the dose of sugammadex is 4 mg/kg; with moderate paralysis, the dose is 2 mg/kg, and the time for reversal is always 2–3 minutes (43). *The reversal with sugammadex is much faster than with neostigmine, and there are no cholinergic side effects*.

A Plea to Avoid Prolonged Paralysis

The experience of being awake while paralyzed is both horrifying and painful (46), and it is imperative to use heavy sedation, and at least some analgesia, while patients are paralyzed. However, it is not possible to evaluate the adequacy of sedation or pain control while a patient is paralyzed without continuous EEG monitoring (which is often not available for this purpose). The inability to ensure adequate sedation and pain control is a major reason to avoid prolonged periods of neuromuscular paralysis whenever possible. This will also reduce the risk of the following complications: (*a*) critical illness myopathy, (*b*) "hypostatic" pneumonia (from pooling of respiratory secretions in dependent lung regions), (*c*) venous thromboembolism, and (*d*) pressure ulcers on the skin.

A FINAL WORD

Inflammation Strikes Again

One of the central themes in this book is the harm inflicted by severe or progressive systemic inflammation in critically ill patients. Inflammatory injury is responsible for the acute respiratory distress syndrome (see Chapter 24) and for many cases of acute kidney injury (see Chapter 34), and inflammation has a pivotal role in the multiorgan failure associated with septic shock (see Chapter 17) and with the post-cardiac arrest period (see Chapter 21). This chapter adds to this list by revealing that inflammation can damage peripheral nerves (i.e., critical illness polyneuropathy) and skeletal muscle (i.e., critical illness myopathy). Considering the swath of

damage that can be inflicted by inflammation, it seems apparent that inflammation is the most lethal force that you (and the patients) will face in the ICU.

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Chapter 47

Acute Stroke in the ICU

Disease makes men more physical, it leaves them nothing but body.

Thomas Mann (*a*)

The focus of this chapter is a cerebrovascular disorder that produces a variety of acute (and often devastating) neurologic deficits. It was first described over 2,400 years ago, and has suffered through a series of inappropriate names, including *acute brain suffering*, *apoplexy*, *stroke*, *cerebrovascular accident* (what accident?), and the most recent embarrassment, *brain attack*. Considering that this disorder is the second leading cause of death worldwide (1), it deserves a better name.

This chapter describes the management of ischemic strokes, as well as strokes caused by spontaneous intracerebral hemorrhage, and subarachnoid hemorrhage. The focus is on management in the ICU, and not on decisions or treatments that occur when the stroke is first suspected (e.g., thrombolytic therapy), which is the purview of neurologists and emergency medicine specialists. Many of the recommendations in this chapter are based on the most recent clinical practice guidelines for each type of stroke (2–5).

ISCHEMIC STROKE

Ischemic strokes account for about 85% of all strokes. Most are the result of atherosclerotic plaques that rupture and trigger a thrombotic occlusion (similar to the pathogenesis of myocardial infarctions), but about 20% are *embolic strokes*. Most emboli are from the left side of the heart, but a small fraction of emboli begin as deep vein thrombosis in the legs, and reach the brain through a patent foramen ovale (see later).

This section describes the management of ischemic strokes after admission to the ICU, and includes general support measures, and special considerations in patients who have received thrombolytic therapy or mechanical thrombectomy. The general support measures that deserve attention are summarized in Table 47.1.

Respiratory Support

Decisions about respiratory support include both oxygenation and ventilation.

Oxygen

Oxygen has two effects that can be deleterious in acute stroke. The first is oxygen's action as a vasoconstrictor in all major vascular beds except the lungs (where it acts as a vasodilator). For the cerebral circulation, inhalation of 100% O_2 results in a 15–30% decrease in cerebral blood flow (6). The second deleterious effect is the ability of oxygen to promote oxidative cell injury via the production of *reactive oxygen species* (7). These two actions would explain the study showing that maintaining an arterial O_2 saturation (SaO_2) above 94% has a negative impact on neurologic outcomes in patients with acute ischemic stroke (8).

RECOMMENDATION: The recent guidelines on stroke management recommend supplemental O_2 only in patients who are hypoxemic (2). However, the same guidelines also state that the SaO_2 should be kept above 94% (2), which is above the hypoxemic level (i.e., <90%), and is at the same level that was associated with worse neurologic outcomes in the study mentioned previously (8). Therefore, it seems wise to *maintain the SaO_2 at 90-92%*, and no higher.

Mechanical Ventilation

Intubation and mechanical ventilation are indicated for: (*a*) patients with impaired consciousness who are unable to protect their airways from aspiration of mouth or gastric secretions, and (*b*) patients with acute respiratory failure (hypoxemic and/or hypercapnic) who cannot be managed otherwise. Remember that *positive pressure ventilation can reduce cerebral perfusion pressure* by increasing intracranial pressure (see Equation (47.1) later in the chapter), so the judicious use of positive pressure ventilation is wise in patients with ischemic stroke.

TABLE 47.1 General Support Measures for Acute Ischemic Stroke

Concern	Recommendations
Oxygen	• Use supplemental O_2 only for patients who are hypoxemic (SaO_2 <90%).
Hypertension	• After thrombolytic Rx or mechanical thrombectomy, keep BP <180/105 for 24 hrs. • Otherwise, lower BP only if >220/120 for the first 72 hrs after admission (unless there is heart failure, etc).
Hyperglycemia	• Lower the blood glucose if >180 mg/dL, and maintain the level at 140–180 mg/dL for 24–48 hrs after admission. • Avoid dextrose-containing IV fluids.
Fever	• Aggressively treat fever for the first 24–48 hrs. • Search for infection as source of fever.
Antiplatelet Therapy	• Start aspirin, 325 mg daily, on day 1 (to prevent early recurrence). • Following thrombolytic Rx, wait 24 hrs before starting aspirin.
Thrombo-prophylaxis	• All patients should receive prophylaxis for deep vein thrombosis using low-molecular-weight heparin. • Following thrombolytic therapy, use sequential compression devices for the first 24 hours.

Hypertension Management

Elevated blood pressure is reported in over 60% of patients with acute stroke (9), and is

considered to be a physiological response that helps to maintain flow in areas surrounding the infarcted area (i.e., the penumbra), where flow is threatened. This is considered to be especially important because cerebral autoregulation is impaired in patients with acute stroke (10), so cerebral flow is highly dependent on blood pressure. This might explain why *blood pressure reduction in the early period following acute stroke has resulted in no apparent improvement in outcomes* (11).

Recommendations

The following recommendations are from the most recent guidelines on stroke management (2).

. For patients who did not receive thrombolytic therapy, blood pressure reduction is advised only at pressures >220/120 mm Hg for the first 72 hours after the stroke (unless there is a condition like left heart failure that requires a more aggressive approach). Furthermore, any decrease in blood pressure should probably not exceed 15% in the first 24 hours after the stroke.

. For patients who have received thrombolytic therapy, the BP should be <180/ 105 mm Hg for 24 hours.

. There is little agreement on the optimal blood pressure following mechanical thrombectomy with successful reperfusion. The guidelines recommend a BP <180/105 mm Hg for 24 hours (2), while other protocols aim for a normal BP (<140/90) after revascularization (12).

TABLE 47.2 Antihypertensive Treatment in Acute Ischemic Stroke

Drug	Dosage and Comments
Labetalol	Dosage: 10 mg as IV bolus, then infuse at 2–8 mg/min; titrate to desired BP. Comment: Equivalent to nicardipine in efficacy and safety.
Nicardipine	Dosage: Infuse at 5 mg/hr, and increase in increments of 2.5 mg/hr, if needed, to 15 mg/hr. Comment: Equivalent to labetalol in efficacy and safety.
Clevidipine	Dosage: Infuse at 1–2 mg/hr, and double the dose rate every 2–5 min, if needed, to 21 mg/hr. Comment: Equivalent to nicardipine in efficacy and safety.

Drug doses from the guidelines in Reference 2. Drug equivalencies from References 12,13.

Antihypertensive Drugs

The recommended drug regimens for blood pressure reduction in the early post-stroke period are included in Table 47.2. *Labetalol* (a combined α- and β-blocker) and *nicardipine* (a calcium channel blocker) have proven to be equivalent for BP control in acute stroke (12). *Clevidipine* (a calcium channel blocker) is not as popular as the other two agents, but has been shown to be equivalent to nicardipine in patients with cerebrovascular disease (13).

Pure β-blockers are not recommended in acute ischemic stroke because they decrease cardiac output, however *metoprolol* (5–10 mg IV every 6 hours) can be used after mechanical thrombectomy with successful reperfusion (2). Nitroprusside should be avoided in acute stroke because it increases intracranial pressure.

Hypotension

Considering that cerebral autoregulation is impaired in acute stroke, prompt correction of hypotension is mandatory, using fluids for hypovolemia and vasopressors, if needed.

. The guidelines for stroke management recommend isotonic saline for volume resuscitation (2), based on studies showing no difference in outcomes between colloid and crystalloid fluids in acute stroke (14). However, the tendency of crystalloid fluids to promote edema formation (see Figure 10.1) seems reason enough to use some colloid fluids (i.e., 5% albumin) for volume resuscitation in acute stroke, especially in patients with hypoalbuminemia.

. For vasopressors, phenylephrine is appropriate for patients with rapid atrial fibrillation, otherwise norepinephrine is an appropriate choice.

. There is no recommendation concerning the target blood pressure in acute stroke, but considering that cerebral autoregulation is impaired, a target pressure that is higher than usual (i.e., greater than a mean arterial pressure of 65 mm Hg) seems warranted.

Glycemic Control

Hyperglycemia occurs in 30–50% of patients (diabetics and nondiabetics) in the first 24 hours after acute stroke, and it has a negative impact on neurologic recovery (15,16). This is very similar to the adverse impact of hyperglycemia on neurologic recovery after cardiac arrest (see Chapter 21). Proposed mechanisms include: (*a*) increased production of lactic acid with local acidosis, (*b*) oxidative stress from glucose-initiated production of reactive oxygen species, and (*c*) disruption of the blood-brain barrier with edema in the penumbra region (15).

The guidelines on stroke management recommend treating hyperglycemia if the blood glucose exceeds 180 mg/dL, with *a target blood glucose in the 140–180 mg/dL rang*e (2). (Since the hyperglycemia is transient, tighter glycemic control runs the risk of hypoglycemia.) *Avoiding dextrose-containing IV solutions is also advised*.

Fever

Fever is reported in up to 60% of patients with acute ischemic stroke (16), and the presence of fever in the first 24–48 hrs a negative influence on both neurologic recovery and mortality (17–19). This is similar to the negative impact of fever on neurologic recovery after cardiac arrest (which is the basis of targeted temperature management, described in Chapter 21).

Source of Fever

Fever typically appears on presentation, or within 72 hours after stroke onset (17), which suggests a noninfectious origin (e.g., from tissue necrosis or intracerebral blood). However, some studies have found infections in a majority of patients with stroke-related fever (20), so a search for infection is warranted for all stroke-related fevers.

Antipyretic Therapy

Prompt decrease in body temperature is indicated for fever in the first 24–48 hours after stroke. The dosing of acetaminophen for antipyresis is described in Chapter 44. *Targeted temperature management does not improve outcomes after ischemic stroke* (21).

Other Measures

Thromboprophylaxis

Acute pulmonary embolism is traditionally cited as a common complication of acute stroke (22), although a 12-year survey of 3 million patients with acute stroke (in Germany) showed only a 0.4% incidence of PE (23). Nevertheless, prophylaxis for deep vein thrombosis is warranted, and low-molecular-weight heparin is the appropriate choice (see Table 5.2 for dosing recommendations). For patients who have received thrombolytic therapy, intermittent pneumatic compression can be used for the first 24 hours.

Antiplatelet Therapy

Aspirin, 325 mg daily, should be started on admission to the ICU (or on day 2 if the patient has received thrombolytic therapy). The aim is to prevent early recurrent stroke, and estimates are that one stroke is avoided for every 100 patients treated (24). Aspirin can be given either orally or by rectal suppository. Anticoagulant therapy is not recommended for acute stroke.

Echocardiography

The following are indications for a cardiac ultrasound in patients with acute ischemic stroke:

. Embolic stroke is suspected (e.g., neuroimaging shows multiple areas of infarction).

. Atrial fibrillation (past or present).

. History of transmural MI (for possible mural thrombus).

. Positive blood cultures (for possible endocarditis).

. History of venous thromboembolism (for possible patent foramen ovale)

. Cryptogenic stroke (same as #5).

Transesophageal ultrasound is the most sensitive method for detecting valvular vegetations or thrombi in the cardiac chambers, but it can be reserved for instances where transthoracic ultrasound (which is much easier to perform) is unrevealing.

Patent Foramen Ovale

As mentioned earlier, an embolic stroke can be the result of a thrombus that originates in the proximal leg veins and passes through a patent foramen ovale (PFO) to embolize in the cerebral circulation. Although uncommon, this scenario is a consideration when there is no apparent predisposing condition for ischemic stroke (e.g., in patients younger than 55 years of age) (25), or in patients who have a history of venous thromboembolism. The test described next is a reliable method for the detection of PFOs.

BUBBLE TEST: This test can be performed with transesophageal or transthoracic echocardiography. For the transthoracic approach, an apical 4-chamber view is preferred. About 10 mL of saline is first agitated to create microbubbles (i.e., by rapidly filling and emptying two syringes attached by a 3-way stopcock). The saline is then rapidly injected, either through a central venous catheter, or a peripheral catheter in the upper arm. After injection, the

microbubbles will become visible in the right side of the heart, and in the presence of a right-to-left intracardiac shunt (from a PFO), the bubbles will appear in the left side of the heart after a few cardiac cycles. This is demonstrated in Figure 47.1 (26).

The presence of a PFO in the setting of an acute ischemic stroke is not evidence of a causal link between the two. However, it is sufficient reason to close the PFO at a later time (if the patient has a satisfactory neurological recovery), using a catheter-based technique.

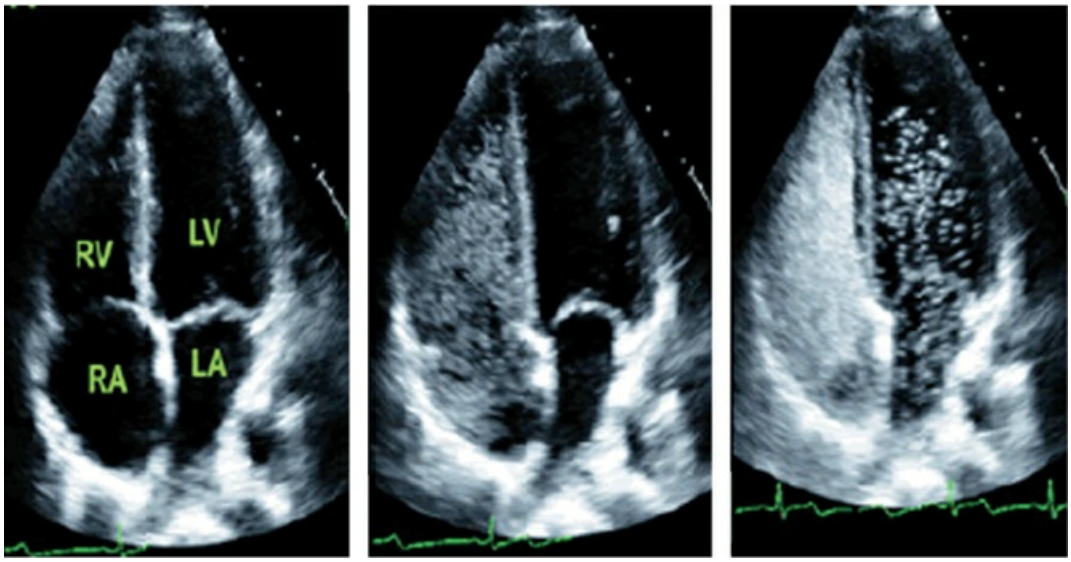

FIGURE 47.1 Transesophageal echocardiography in a patient with acute ischemic stroke, showing microbubbles (from the injection of agitated saline) moving from the right to left side of the heart. This is evidence of a right-to-left shunt from a patent foramen ovale. Images adapted from Reference 26.

CNS Complications

The central nervous system complications of acute stroke, (and stroke management), include intracerebral hemorrhage, cerebral edema, and seizures.

Intracerebral Hemorrhage

The most devastating complication of stroke management is shown in Figure 47.2 (27). The CT images in this figure are from a patient with an acute ischemic stroke who experienced an acute deterioration in mental status five hours after receiving thrombolytic therapy with tissue plasminogen activator (tPA). A repeat CT image at that time showed a massive intracerebral hemorrhage with mass effect.

The incidence of symptomatic intracerebral hemorrhage following thrombolytic therapy for acute stroke is 6.4% to 8.8% (28,29). Risk factors include advanced age, blood pressure above 180/105, and a stroke that involves more than one-third of a cerebral hemisphere. The risk of hemorrhage is the reason that patients who receive thrombolytic therapy are admitted to an ICU or stroke unit for 24 hours, where it is possible to closely monitor neurologic status and blood pressure. Anticoagulants and antiplatelet agents are also withheld for the first 24 hours after thrombolytic therapy.

MANAGEMENT: There is no validated treatment for hemorrhagic transformation of acute stroke,

but the following measures are recommended in the most recent guidelines on stroke management (2).

. Cryoprecipitate (10 Units) is recommended as a source of fibrinogen, and the dose can be repeated if the serum fibrinogen is below 200 mg/dL (2). However, cryoprecipitate must be thawed, which delays treatment by at least 20 minutes. A better choice would be *fibrinogen concentrates*, which have two advantages over cryoprecipitate (30): (*a*) thawing is not necessary, so treatment can be started immediately, and (*b*) the concentration of fibrinogen is more consistent (at 20 g/L).

. If cryoprecipitate is not immediately available, tranexamic acid (an antifibrinolytic agent) can be given in a dose of 1,000 mg IV over 10 minutes (2).

. A neurosurgery consultation is warranted (to consider decompression hemicraniectomy).

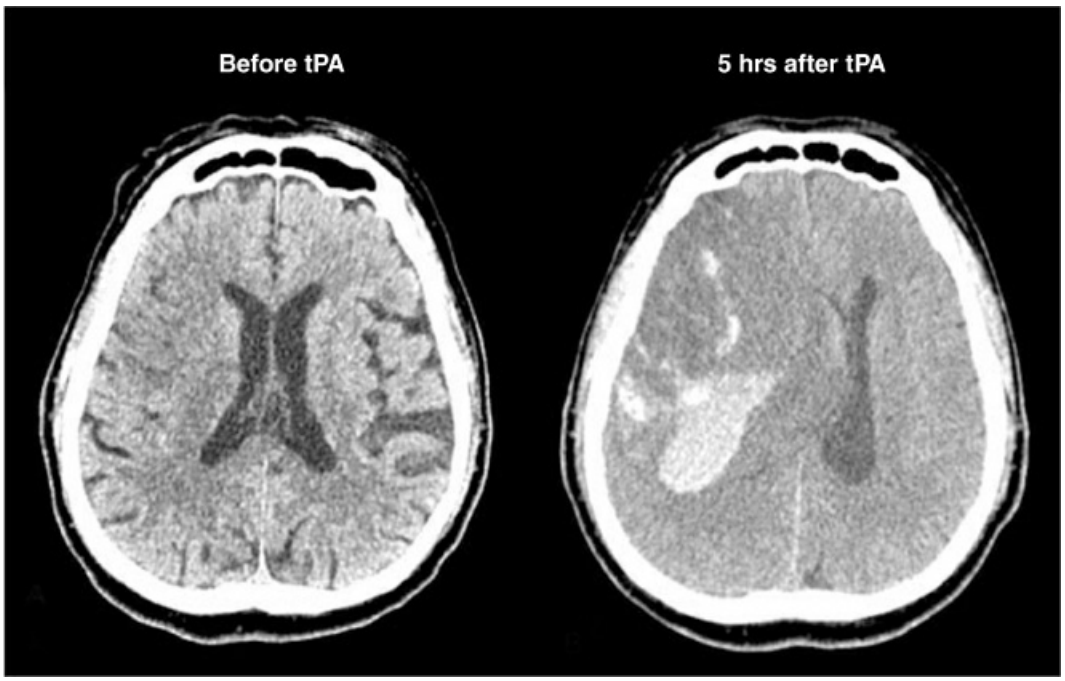

FIGURE 47.2 Noncontrast CT images of the brain from a patient who experienced an abrupt deterioration in mental status 5 hours after receiving thrombolytic therapy with tissue plasminogen activator (tPA). The CT scan on the right shows a massive intracerebral hemorrhage (hyperdense areas) with midline shift. Images from Reference 27.

Cerebral Edema

Hemorrhage and cerebral edema are the principal determinants of poor outcomes after acute stroke. There are two types of cerebral edema: *cytotoxic edema*, which is the result of cell necrosis, and *vasogenic edema*, which involves loss of vascular control mechanisms, and results in disruption of the blood-brain barrier. The larger the ischemic area, the more extensive the cerebral edema.

MANAGEMENT: Intracranial pressure (ICP) monitoring is not recommended for acute ischemic stroke that is complicated by cerebral edema (2). Instead, monitoring neurologic symptoms and

signs is considered adequate. When cerebral edema causes a deterioration in neurologic status, *hypertonic saline* can be used to lower the ICP (31,32). Mannitol is also capable of lowering the ICP, but it is not as effective as hypertonic saline in patients with an elevated ICP after stroke (33). There is no evidence that hypertonic therapy alters the outcome in acute stroke (31,32).

There are a number of different hypertonic saline solutions, and Table 47.3 shows some of the characteristics of the different solutions, including the bolus doses recommended for lowering the ICP (32). The more concentrated solutions are appealing because they are effective at a lower volume. Bolus dosing of hypertonic saline is preferred to a continuous infusion because the effect occurs more rapidly. The target plasma sodium is typically 145–155 mEq/L (32).

TABLE 47.3 Hypertonic Saline Solutions for Treating Cerebral Edema

	3% NaCL	5% NaCL	7.5% NaCL	14.6% NaCL	23.4% NaCL
$[Na^+]$ (mEq/L)	513	856	1,293	2,500	4,000
Osmolality (mOsm/L)	1,027	1,711	2,566	5,000	8,008
Commercially Available	Yes	Yes	No	Yes	Yes
Bolus Dose for Cerebral Edema	250 mL or 5 mL/kg	100 mL	100 mL or 2–4 mL/kg	24–48 mL	30 mL or 0.68–2 mL/kg

From Reference 32.

Seizures

About 20% of patients have a symptomatic seizure in the first week after an ischemic stroke, and about one-quarter of the seizures recur at some time in the ensuing 4 years (34). Therefore, anticonvulsant therapy (e.g., with levetiracetam) is recommended for post-stroke seizures, and it should be continued after discharge. Seizure prophylaxis is not recommended in the early period following ischemic stroke (2).

SPONTANEOUS INTRACEREBRAL HEMORRHAGE

Spontaneous (non-traumatic) intracerebral hemorrhage accounts for about 10–15% of acute strokes, and the predisposing conditions include hypertension and systemic anticoagulation. The prognosis with this type of stroke is typically less favorable than with ischemic strokes: i.e., about half of the patients do not survive for 30 days (35), and two-thirds of the survivors have significant neurologic deficits (36). The CT image in Figure 47.3 helps to understand why the prognosis is poor following intracerebral hemorrhage.

Reversing Antithrombotic Agents

Rapid deterioration is common in the early hours after intracerebral hemorrhage (ICH), and is attributed to expansion of the hematoma (3). Therefore, the first concern is to arrest growth of the hematoma, and to this end, prompt reversal of ongoing antithrombotic therapy is mandatory. The reversal agents and dosing regimens for the commonly used antithrombotic agents are presented in Tables 47.4 and 47.5 (36–38).

Warfarin

Anticoagulation with warfarin can be reversed by 4-factor prothrombin complex concentrate (PCC) (so named because it contains Factors II, VII, IX, and X), which can normalize the INR much faster than fresh frozen plasma (FFP), and at a much smaller volume. In one study of excessive bleeding from warfarin, 4-factor PCC normalized the INR within 30 minutes in 60% of the patients, while FFP achieved the same feat in only 9% of patients (39). Vitamin K is given along with the 4-factor PCC, but the effect is much slower (i.e., the effect begins at about 2 hours, and is maximal at 24 hours) (3). The dosing of 4-factor PCC is determined by the INR, as shown in Table 47.4.

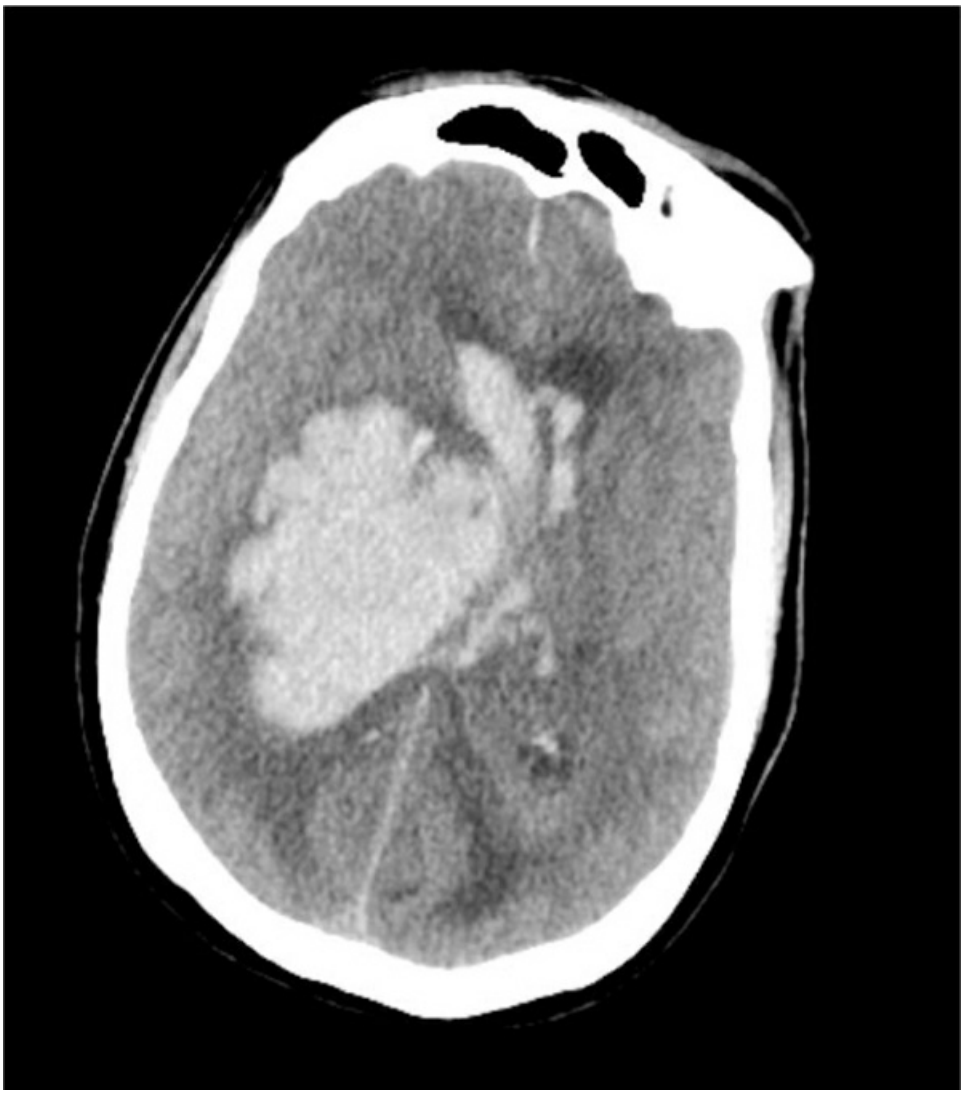

FIGURE 47.3 Noncontrast CT image showing a large hyperdense intracerebral hematoma that occupies about one-half of the volume of the right side of the brain. The bleeding also extends into the ventricles, which creates the risk of an obstructive hydrocephalus.

Dabigatran

The anticoagulant effect of the direct thrombin inhibitor dabigatran can be reversed in 10–30 minutes by *idarucizumab* (Praxbind®), a monoclonal antibody that readily binds to dabigatran. (See Table 47.4 for the dosing.) An alternative approach is 4-factor PCC in high doses (50 IU/kg) (3), although there is limited experience with this approach.

Factor Xa Inhibitors

The anticoagulant effects of the Factor Xa inhibitors, apixaban and rivaroxaban, can be blocked by *andexanet alfa*, which is a dummy Factor Xa that binds the drugs but produces no anticoagulation. The dosing of this agent is presented in Table 47.5, and is determined by the anticoagulant and dosage, and the time elapsed from the last dose (37). When andexanet is given to patients with excessive bleeding (including intracerebral bleeding) from apixaban or rivaroxaban, there is a 90% reduction in anti-Xa activity after about 10 minutes, and hemostasis

is fully restored after 12 hours (40). Andexanet has one adverse effect that deserves mention: i.e., about 10% of patients develop venous thromboembolism (40). If andexanet is not available, 4-factor PCC in a high dose (50 IU/kg) is recommended as an alternative treatment (3).

TABLE 47.4 Reversal of Antithrombotic Agents in Intracranial Hemorrhage

Antithrombotics	Reversal Agents & Dosage
Warfarin	• Vitamin K: 10 mg IV, plus • 4-factor PCC, dosing as follows: INR ..... Dose 2–4 ..... 25 U/kg 4–6 ..... 35 U/kg >6 ..... 50 U/kg
Dabigatran (Pradaxa®)	• Idarucizumab 2.5 mg IV bolus and repeat within 15 minutes. • Consider high-dose 4-factor PCC (50 IU/kg) if idarucizumab is not available.
Apixaban (Eliquis®) or Rivaroxaban (Xarelto®)	• Andexanet alfa - see Table 47.5 for dosing. • Consider high-dose 4-factor PCC (50 IU/kg) if andexanet is not available.
Unfractionated Heparin	• Protamine sulfate: 1 mg per 100 units of heparin given at last dose.
Enoxaparin (Lovenox®)	• Protamine sulfate: 1 mg per 1 mg of enoxaparin at last dose. Less effective than against unfractionated heparin.
Aspirin, Clopidogrel	• Desmopressin: 3 µg/kg subQ or IV. Can repeat once.

From References 36,37. PCC = prothrombin complex concentrate.

TABLE 47.5 Dosing Recommendations for Andexanet Alfa

Regimen	Criteria	Dosage
Low-Dose Regimen	Last apixaban dose ≤5 mg or rivaroxaban dose ≤10 mg. or time since last dose ≥8 hrs.	Start with IV bolus of 400 mg (at 30 mg/min), then infuse at 4 mg/min for up to 120 min.
High-Dose Regimen	Last apixaban dose >5 mg or rivaroxaban dose >10 mg. or time since last dose <8 hrs or unknown.	Start with IV bolus of 800 mg (at 30 mg/min), then infuse at 8 mg/min for up to 120 min.

From Reference 37.

Antiplatelet Agents

Aspirin and clopidogrel produce irreversible inhibition of platelet adhesiveness that lasts for the lifetime of the exposed platelets (i.e., 7–10 days), but this effect can be antagonized by desmopressin (41), which promotes the release of von Willebrand factor from endothelial cells.

Other Measures

Many of the measures described for ischemic stroke (e.g., blood pressure control, glycemic control) are also recommended for patients with spontaneous ICH (3).

. High blood pressure can be especially harmful in acute hemorrhage, and maintaining a systolic blood pressure below 140 mm Hg is recommended (3).

. Prophylaxis for deep vein thrombosis should begin at the time of admission, and sequential compression devices should be used for prophylaxis in the first 24 hours. Thereafter, the decision to begin prophylaxis with one of the heparin preparations will depend on the clinical condition of the patient (stable or unstable).

. Seizure prophylaxis is not recommended in patients with ICH (3). However, symptomatic seizures are reported in about 15% of patients in the first week after ICH (3), and these patients should receive anticonvulsant therapy (e.g., with levetiracetam).

. Patients with ICH who have impaired consciousness should be evaluated for nonconvulsive status epilepticus with continuous EEG monitoring for 24–36 hours, if available.

. A neurosurgery consult is warranted in most cases of ICH, especially those with large or expanding hematomas, or bleeding that has extended into ventricles (as in Figure 47.3). Intraventricular blood often leads to obstructive hydrocephalus, and requires insertion of a catheter into the ventricles for drainage, and for intraventricular thrombolytic therapy (42). The intraventricular catheter can also be used to monitor the intracranial pressure.

Intracranial Pressure

The clinical practice guideline on spontaneous ICH (3) recommends intracranial pressure (ICP) monitoring in the following situations: (*a*) patients with a Glasgow Coma Score of ≤8 (see Table 45.5), (*b*) blood in the ventricular system, and (*c*) clinical evidence of transtentorial herniation (e.g., unilateral pupillary dilation). The ICP should then be maintained below 20 mm Hg (usually by periodically draining fluid from the intraventricular catheter) (3,43). The ICP measurement also allows an estimation of the *cerebral perfusion pressure*.

Cerebral Perfusion Pressure

The cerebral perfusion pressure (CPP) is the driving pressure for flow in the cerebral circulation, and is the difference between the mean arterial pressure (MAP) and the intracranial pressure (ICP); i.e.,

$$CPP = MAP - ICP \text{ (mm Hg)} \qquad (47.1)$$

The influence of CPP on cerebral blood flow is influenced by the vascular resistance in the cerebral circulation, and the presence or absence of cerebral autoregulation. *A CPP of 50–70 mm Hg is considered a reasonable goal in patients with ICH* (44).

SUBARACHNOID HEMORRHAGE

The most devastating type of stroke occurs when a saccular aneurysm in one of the cerebral arteries ruptures, resulting in the accumulation of blood in the subarachnoid space (see Figure 47.4) (45). The severity of this condition is demonstrated by the following observations:

. For patients who experience an aneurysmal SAH, as many as 25% will succumb before

reaching the hospital (4), and another 20% will not survive the hospitalization (46).

. Six months after hospital admission, 35% of the patients will be dead or disabled (46).

. Combining these observations indicates that over half of the patients with an aneurysmal SAH will die or become disabled within 6 months.

SAH also affects a younger age group than the other types of stroke (4). In one survey, the mean age of SAH victims was 55 years (47). Thus, SAH can remove people from their source of income, which has serious implications for families.

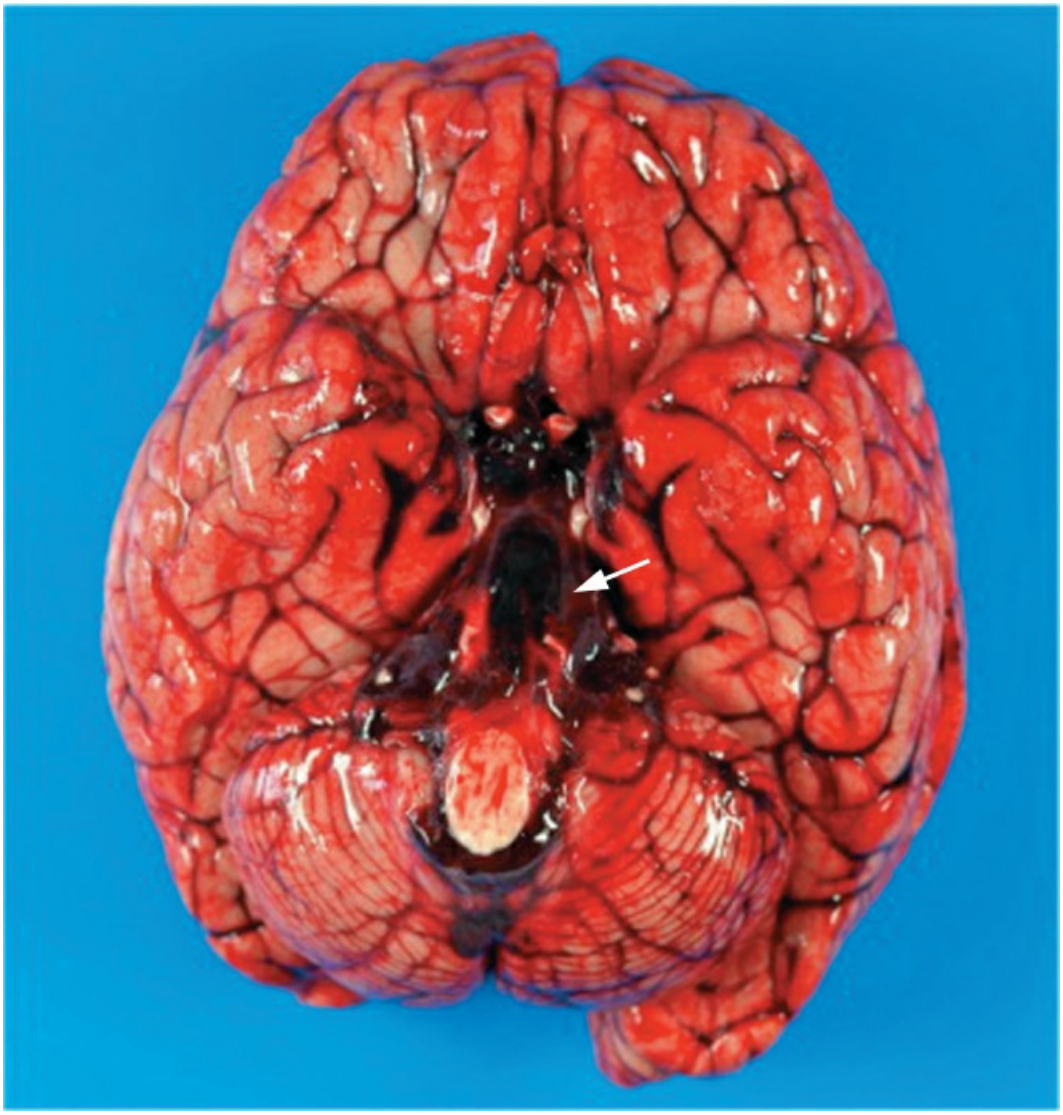

FIGURE 47.4 Postmortem specimen showing blood in the subarachnoid space at the base of the brain. The source of the subarachnoid hemorrhage was rupture of a saccular aneurysm in the basilar artery, which is located under the hematoma, as indicated by the arrow. Image from Reference 45.

Sources of Tissue Injury

The poor outcomes in aneurysmal SAH are explained by the multiple sources of tissue injury, as

summarized below.

. The presence of blood in the subarachnoid space triggers an intense inflammatory response that damages the blood brain barrier (which promotes vasogenic cerebral edema) and produces oxidative damage in neurons and glial cells (which produces cytotoxic cerebral edema) (48). The iron in extravasated blood very likely has role in the damaging effects of subarachnoid hemorrhage, because iron promotes the production of highly-toxic hydroxyl radicals (see Figure 25.6), and free iron can promote cell death by oxidizing membrane lipids; a process known as *ferroptosis* (49).

. Blood in the subarachnoid space blocks the flow of cerebrospinal fluid, which often leads to an obstructive hydrocephalus and increased intracranial pressure.

. In about one-third of patients, there is a second phase of tissue injury that is ischemic in nature, and occurs between days 4 and 14 (4). This *delayed cerebral ischemia* (DCI) is considered a major source of morbidity and mortality, and is attributed to vasospasm and thrombotic occlusion of cerebral arteries and arterioles (50).

. SAH is often associated with inflammatory injury in organs other than the brain. Common associated conditions include the acute respiratory distress syndrome (ARDS), and acute kidney injury (AKI) (4).

Management

The management of SAH is directed at the sources of injury just mentioned. Many of the measures are similar to those described for intracerebral hemorrhage.

Immediate Concerns

The most immediate concern is to reduce the risk of bleeding from the ruptured aneurysm. This requires attention to the following:

. Ongoing antithrombotic therapy should be reversed as soon as possible (see Tables 47.4 and 47.5).

. Correction of hypertension is warranted, if necessary. The clinical practice guidelines for SAH do not recommend a target blood pressure, but there is evidence that rebleeding is uncommon if the systolic BP is below 140 mm Hg (51). Therefore, a systolic BP of ≤140 mm Hg is a reasonable target. Blood pressure reduction should not increase the cardiac output (since this could promote bleeding), so labetalol is an appropriate antihypertensive agent (See Table 47.2 for dosing instructions).

. Antifibrinolytic agents (e.g., tranexamic acid) are not effective in preventing rebleeding (4), and thus are not recommended.

Attention to the Aneurysm

The best way to prevent rebleeding is to obliterate the ruptured aneurysm (e.g., with clips), and you will need a neurosurgeon or interventional radiologist for this task. This may be difficult to pursue if the patient is unstable, but outcomes are improved if corrective action is taken within 3 days of the event (52), and you are advised not to delay this for longer than 7–10 days (4).

Delayed Cerebral Ischemia

The delayed cerebral ischemia (DCI) mentioned earlier, which can appear 4 to 14 days after SAH, is considered a major source of morbidity and mortality. The following measures are recommended to reduce the risk of DCI (4).

. The calcium channel blocker *nimodipine* is recommended orally in a dose of 60 mg every 4 hours, starting as soon as possible after the diagnosis of SAH, and continuing for 3 weeks (4). This dosing regimen has been shown to reduce neurologic deficits, but has no impact on survival (53). The intravenous route is not recommended because of the risk of hypotension.

. Monitoring to detect the onset of DCI can be carried out in several ways. Clinical signs of DCI can include a new focal deficit, or a drop of 2 points in the Glasgow Coma Score (see Table 45.5), so frequent neurologic assessments are advised. CT angiography (CTA) and transcranial Doppler ultrasound (measures flow velocity usually in the middle cerebral artery) are both useful, with sensitivities of about 90% for the detection of cerebral vasospasm (4).

. For severe cases of vasospasm, intra-arterial vasodilators or angioplasty should be considered.

Intracranial Pressure

Recommendations for intracranial pressure (ICP) monitoring are the same as described for intracerebral hemorrhage. Drainage catheters are placed in patients who develop hydrocephalus, and these catheters can be used to monitor the ICP. In general, the ICP is kept below 20 mm Hg with periodic drainage of cerebrospinal fluid through the catheter. Patients who survive will require permanent shunting of cerebrospinal fluid into the abdominal cavity.

General Measures

General support is similar to that described for the other types of stroke, and includes the following:

. The incidence of venous thromboembolism in SAH is as high as 25% (4), so thromboprophylaxis is mandatory. Prophylactic doses of enoxaparin (40 mg subQ daily) have been used safely after aneurysm repair (4).

. Fever is common after SAH, and it has a negative influence on outcomes (54). However, fever suppression with antipyretic agents and cooling devices have not improved outcomes (4).

. Hyperglycemia in the first 72 hours after SAH has a negative impact on outcomes (4), but there is no recommendation about glycemic control in the SAH guidelines (4).

. Hyponatremia is reported in 35% of patients with SAH (55), and is possibly a result of cerebral salt wasting. However, the clinical significance of this has yet to be determined.

A FINAL WORD

Where's the Beef?

The ability of thrombolytic therapy and mechanical thrombectomy to re-establish flow has created high expectations for the management of ischemic strokes, and these expectations fueled

a massive effort to create “stroke centers” in major hospitals, with specialized “stroke teams” to direct the management of acute stroke. The following is an accounting of what this effort has accomplished. (The following numbers are from References 56–60.)

Number of strokes each year in the United States. 795,000
Number of ischemic strokes (85%). 676,000
Number of stroke patients who receive lytic therapy (5%) and/or
mechanical thrombectomy (2%): i.e., 7% of 696,000. 47,320
Number of patients who benefit from reperfusion therapy (1 in 9). 5,258
Percent of strokes that benefit from reperfusion therapy (5,258/676,000). . . 0.8%
Enough said.

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Section XV

NUTRITION & METABOLISM

What is food to one man, may be fierce poison to others.

Lucretius
(99–55 BC)

Chapter 48

Nutritional Requirements

The more impure bodies are fed,. the more diseased they will become

Hippocrates *Aphorisms*

The fundamental goal of nutritional support is to provide the daily nutrient and energy needs of each patient. This chapter describes what is known about providing those needs, according to the most recent clinical practice guidelines (1–3) and expert commentaries (4,5) on the subject. However, it is important to mention at the outset that it is impossible to accurately determine the nutritional needs of critically ill patients, or whether we should be feeding "impure bodies", at all. This latter point (i.e., the notion that feeding critically ill patients can be harmful) is the focus of the very last section of this chapter.

DAILY ENERGY EXPENDITURE

Oxidation of Nutritional Fuels

The energy from the sun is stored in the covalent carbon bonds that hold organic (carbon-based) molecules together. Carbon bonds have differing amounts of stored energy (e.g., double bonds have more energy than single bonds), and molecules that are rich in high-energy carbon bonds are known as *fuels*. The energy in organic fuels is released by a chemical reaction with oxygen, which breaks the carbon bonds and releases the energy. This reaction is known as *oxidation*.

The oxidative metabolism of *nutritional fuels* (i.e., lipids, proteins, and carbohydrates) releases the stored energy and utilizes it to sustain life. This process consumes oxygen, and generates carbon dioxide, water, and heat. The quantities involved in the oxidation of each type of nutritional fuel are shown in Table 48.1. The following points deserve mention.

. The energy yield from nutritional fuels is expressed as heat production (in kilocalories or kcal per gram of fuel).

. The energy yield is highest with lipids (9.1 kcal/g) and lowest with carbohydrates (3.7 kcal/g).

. The respiratory quotient (RQ) is a measure of the CO_2 production (VCO_2) relative to the O_2 consumption (VO_2) (i.e., RQ = VCO_2/VO_2). Carbohydrates have the highest RQ (1.0), and

lipids have the lowest (0.7).

TABLE 48.1 The Oxidation of Nutritional Fuels

Fuel	O_2 Consumption	CO_2 Production	RQ†	Energy Yield
Lipids	2.00 L/g	1.40 L/g	0.7	9.1 kcal/g
Proteins	0.96 L/g	0.78 L/g	0.8	4.0 kcal/g
Carbohydrates	0.74 L/g	0.74 L/g	1.0	3.7 kcal/g

†RQ is "respiratory quotient", and is the ratio of CO_2 production (VCO_2) to O_2 consumption (VO_2): i.e., $RQ = VCO_2/VO_2$.

The oxidative metabolism of all three nutritional fuels determines the whole body VO_2, VCO_2, and RQ. The VO_2 and VCO_2 can be used to determine the energy expenditure (see next) while the whole-body RQ indicates the balance of energy being provided by the nutritional fuels (e.g., an RQ of 1.0 indicates that carbohydrates are the predominant fuel source).

Indirect Calorimetry

It is not possible to directly measure energy expenditure (i.e., heat production) in hospitalized patients. However, it is possible to calculate the resting energy expenditure (REE) from the whole-body VO_2 and VCO_2 using the following equation (6):

$$\text{REE (kcal/min)} = (3.6 \times VO_2) + (1.1 \times VCO_2) - 61 \qquad (48.1)$$

This is the principle of *indirect calorimetry*, which measures the whole-body VO_2 and VCO_2 to derive the energy expenditure.

Methodology

Indirect calorimetry is performed with "metabolic carts" that measure whole-body VO_2 and VCO_2 at the bedside by measuring the concentrations of O_2 and CO_2 in inhaled and exhaled gas. This can be done in spontaneously breathing patients (using a special canopy placed over the patient's head) and during mechanical ventilation (by placing O_2 and CO_2 sensors in line with the ventilator tubing) (7). Steady-state measurements are obtained for 15–30 minutes to determine the REE (kcal/min), which is then multiplied by 1,440 (the number of minutes in 24 hours) to derive the daily energy expenditure (kcal/24 hr). Clinical studies have shown that REE measurements obtained over 30 minutes and extrapolated to 24 hours are equivalent to REE measurements performed for 24 hours (8). The oxygen sensor in the newest indirect calorimetry devices is accurate to inhaled O_2 concentrations up to 70% (9), which is an improvement over the prior upper limit of 60% (10). However, there is still the risk that indirect calorimetry will be unreliable when the inhaled O_2 concentration is above 70%.

All clinical practice guidelines recommend indirect calorimetry for determining the daily energy needs in critically ill patients (1–3). However, indirect calorimetry is not universally

available, because the equipment is expensive, and it requires trained personnel to operate. When indirect calorimetry is not available, the REE can be estimated, as described next.

A Simple Formula

There are more than 200 cumbersome equations available for estimating daily energy requirements, but none is considered more predictive than the following relationship:

$$\text{REE (kcal/day)} = 25 \times \text{body weight (kg)} \qquad (48.2)$$

This simple predictive relationship is considered suitable for estimating daily energy requirements when indirect calorimetry is not available (2,3). Actual body weight is used unless it is 25% higher than ideal body weight. When actual body weight is more than 125% of ideal body weight, the adjusted body weight is recommended, using the following equation (11):

$$\text{Adjusted weight (kg)} = [(\text{actual} - \text{ideal weight}) \times 0.25] + \text{ideal weight} \qquad (48.3)$$

Recommendations

Some form of nutrition support should be provided within 24–48 hours of ICU admission (1–3). However, the most recent guidelines recommend that nutrition support should begin at REE levels that are less than the measured or estimated REE (1,3). The basis for this recommendation is evidence that endogenous nutritional adjustments (e.g., increased gluconeogenesis) are operative in the early stages of acute illness, and adding a normal nutritional intake to these adjustments results in overfeeding (which can result in hyperglycemia and lipogenesis) (12). In patients who are malnourished at the outset, avoiding aggressive early nutrition will also reduce the risk of the refeeding syndrome (13).

The following recommendations are from the European guidelines for nutrition support (3):

- If indirect calorimetry is used to measure REE, then no more than 70% of the REE should be provided for the first 3 days of nutrition support. Thereafter, the REE can be gradually increased to 100% over the remainder of the first week.
- If predictive equations are used to estimate REE, then no more than 70% of the REE should be provided for the first 7 days of nutrition support.
- In patients who require norepinephrine doses >0.2 μg/kg/min (>14 μg/min in a 70 kg adult), a daily caloric intake of 10–15 kcal/kg/day should be considered for 7 days, or until the clinical condition improves (5).

SUBSTRATE REQUIREMENTS

The daily energy requirement should be provided by nonprotein calories from carbohydrates and lipids, while protein intake is used to maintain essential enzymatic and structural proteins.

Carbohydrates

Standard nutrition regimens use carbohydrates to provide about 70% of the nonprotein calories. The human body has limited carbohydrate stores (Table 48.2), and daily intake of carbohydrates

is considered necessary to ensure proper functioning of the central nervous system, which uses about 100–120 grams of glucose daily (3). Therefore, a daily carbohydrate intake of at least 130 grams is advised (3).

Physiological stress is common in critically ill patients, and this promotes insulin resistance and hyperglycemia (14). In addition, excessive carbohydrate intake promotes CO_2 production (see Table 48.1) and lipogenesis (14). For these reasons, carbohydrate intake should be limited to no more than 5 mg/kg/min (3), which is about 500 grams daily in a 70 kg adult.

TABLE 48.2 Endogenous Fuel Stores in Healthy Adults

Fuel Source	Amount (kg)	Energy Yield (kcal)
Adipose Tissue Fat	15.0	141,000
Muscle Protein	6.0	24,000
Total Glycogen	0.09	900 ------ Total: 165,000

Data from Cahill GF. Jr. N Eng J Med 1970; 282:668–675.

Lipids

Standard nutrition regimens use lipids to provide approximately 30% of the daily energy needs. Dietary lipids have the highest energy yield of the three nutrient fuels (Table 48.1), and lipid stores in adipose tissues represent the major endogenous fuel source in healthy adults (Table 48.2).

Linoleic Acid

Dietary lipids are triglycerides, which are composed of a glycerol molecule linked to three fatty acids. The only dietary fatty acid that is considered essential (i.e., must be provided in the diet) is linoleic acid, a long chain, polyunsaturated fatty acid (PUFA). A deficient intake of this essential fatty acid produces a clinical disorder characterized by a scaly dermopathy, cardiac dysfunction, and increased susceptibility to infections (15). This disorder is prevented by providing 0.5% of the dietary fatty acids as linoleic acid. Soybean oil is used as the source of linoleic acid in most nutritional support regimens.

Propofol

Propofol, an intravenous anesthetic agent that is popular for short-term sedation in the ICU, is mixed in a 10% lipid emulsion that provides 1.1 kcal/mL (2,3). As a result, *the calories provided by propofol infusions must be considered when calculating the nonprotein calories in a nutrition support regimen*. Propofol infusions can also promote hypertriglyceridemia (16), so triglyceride levels should be monitored during prolonged infusions of propofol.

Excessive Lipid Intake

Excessive intake of lipids, especially PUFAs (which are highly oxidizable), can lead to oxidative damage in tissues, especially the lungs (17), and can impair immune function (3). To prevent

lipid overload, *the recommended maximum lipid intake is 1.5 grams/kg per day* (3). (*Note:* It is also possible to adjust the type of lipid intake to reduce the risk of inflammatory injury. This is described in chapters 49 and 50.)

Protein Requirements

The normal protein requirement is 0.8–1.0 grams/kg/day in healthy patients, but because hypercatabolism is common *in critically ill patients, a protein intake of 1.2– 2.0 grams/kg/day is recommended* (1,2).

Nitrogen Balance

The adequacy of protein intake can be evaluated with the nitrogen balance; i.e., the difference between intake and excretion of protein-derived nitrogen. However, *patients should be in a stable condition before this evaluation is performed.*

. *Nitrogen Excretion:* Two thirds of the nitrogen derived from protein breakdown is excreted in the urine (18), and about 85% of this nitrogen is contained in urea (the remainder is in ammonia and creatinine). Thus, the urinary urea nitrogen (UUN), measured in grams excreted in 24 hours, represents the bulk of nitrogen derived from protein breakdown. The remainder of the protein-derived nitrogen (usually about 4–6 grams/day) is excreted in the stool. Therefore, protein-derived nitrogen excretion can be expressed as follows:

$$\text{Nitrogen Excretion (g/24 h)} = \text{UUN} + (4\text{–}6) \qquad (48.4)$$

In the presence of diarrhea, non-urinary nitrogen losses cannot be estimated accurately, and nitrogen balance determinations are unreliable.

. *Nitrogen Intake:* Protein is 16% nitrogen, so each gram of protein contains 1/6.25 grams of nitrogen. Therefore, protein-derived nitrogen intake is derived as follows:

$$\text{Nitrogen Intake (g/24 h)} = \text{Protein Intake (g/24 h)}/6.25 \qquad (48.5)$$

. *Nitrogen Balance:* The equations for nitrogen intake and nitrogen excretion are combined to determine the daily nitrogen balance.

$$\text{Nitrogen Balance (g/24 h)} = \text{Protein Intake}/6.25 - [\text{UUN} + (4\text{–}6)] \qquad (48.6)$$

. The goal of nutritional support is a positive nitrogen balance of 4–6 grams.

Nitrogen Balance & Nonprotein Calories

The first step in achieving a positive nitrogen balance is to provide enough nonprotein calories to spare proteins from being degraded to provide energy. This is demonstrated in Figure 48.1. When the daily protein intake is constant, the nitrogen balance becomes positive only when the intake of nonprotein calories is sufficient to meet the daily energy needs (i.e., the REE). Therefore, *increasing protein intake will not achieve a positive nitrogen balance unless the intake of nonprotein calories is adequate*.

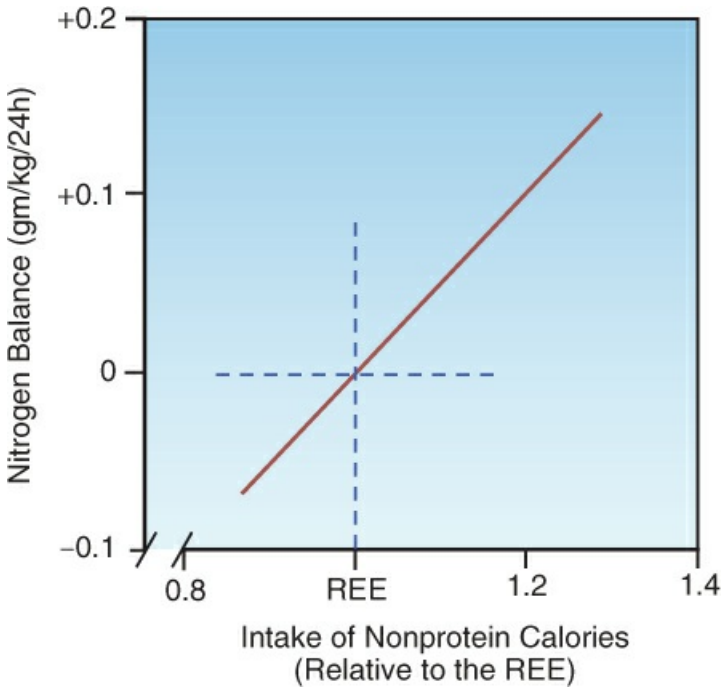

FIGURE 48.1 Relationship between nitrogen balance and the daily intake of nonprotein calories relative to daily calorie requirements. Protein intake is constant. REE = resting energy expenditure.

VITAMIN REQUIREMENTS

Thirteen vitamins are considered an essential part of the daily diet, and Table 48.3 shows the recommended daily requirement for these vitamins in healthy adults. Daily vitamin requirements are likely to be higher in critically ill patients, and will also vary in individual patients. The following is a description of vitamin deficiencies that deserve particular attention in critically ill patients.

TABLE 48.3 Daily Vitamin Requirements in Adults, Ages 51–70

Vitamin	Men	Women*
Vitamin A	900 µg/d	700 µg/d
Vitamin C	90 mg/d	75 mg/d
Vitamin D	600 IU/d	600 IU/d
Vitamin E	15 mg/d	15 mg/d
Vitamin K	120 µg/d	90 µg/d
Thiamine	1.2 mg/d	1.1 mg/d
Riboflavin	1.3 mg/d	1.1 mg/d
Niacin	16 mg/d	14 mg/d

Pyridoxine	1.7 mg/d	1.5 mg/d
Folate	400 µg/d	400 µg/d
Vitamin B_{12}	2.4 µg/d	2.4 µg/d
Pantothenic Acid	5 mg/d	5 mg/d
Biotin	30 µg/d	30 µg/d

From the National Institutes of Health, Office of Dietary Supplements. Available at ods.od.nih.gov/HealthInformation/nutrientrecommendations.aspx. Accessed 7/2/2024 *Does not include pregnant or lactating women.

Thiamine Deficiency

Thiamine (vitamin B_1) plays an essential role in carbohydrate metabolism, because thiamine is converted to thiamine pyrophosphate, which is a cofactor for pyruvate dehydrogenase, the enzyme that allows pyruvate to enter mitochondria and generate high-energy ATP molecules (see Figure 9.5) (19). Thiamine deficiency thus creates an energy deficit from impaired glucose metabolism. (There are other metabolic consequences of thiamine deficiency, which are beyond the scope of this text.) Healthy adults have a limited store of thiamine (about 30 mg), which is depleted after 2–3 weeks in the absence of thiamine intake (19). The normal thiamine requirement is about 1 mg/day in healthy adults (see Table 48.3).

Predisposing Factors

There are several conditions in ICU patients that promote thiamine deficiency, and the major ones are listed in Table 48.4. Alcoholism is considered the major cause of thiamine deficiency; an effect that is attributed to alcohol's ability to inhibit thiamine absorption from the GI tract (20). Thiamine deficiency has also been reported in as many as 70% of ICU patients with septic shock (21). Other predisposing factors that are common in ICU patients include the chronic use of furosemide (22), which promotes thiamine excretion by the kidneys, and magnesium depletion (23), which inhibits the conversion of thiamine to thiamine pyrophosphate (24). Thiamine deficiency has also been reported following gastric surgery for obesity (25), presumably as a result of impaired thiamine absorption from the GI tract.

REFEEDING: Patients who are admitted with borderline thiamine stores can become thiamine deficient when they receive a glucose load (usually from nutrition support regimens). This is similar in principle to the refeeding syndrome, although it is a distinct entity (26).

TABLE 48.4 Thiamine Deficiency

Predisposing Factors	Clinical Manifestations
• Alcohol Abuse • Malnutrition • Septic Shock • Furosemide • Mg^{++} Depletion	• Cardiomyopathy (Beriberi) • Encephalopathy (Wernicke's) • Peripheral Neuropathy • Lactic Acidosis

Treatment[†]

1. 500 mg thiamine IV every 8 hours for 2–3 days, then
2. 250 mg thiamine IV once daily for 3–5 days, then
3. 100 mg thiamine PO three times daily for 1–2 weeks, then
4. 100 mg thiamine PO once daily for maintenance therapy.

Clinical Manifestations

The clinical manifestations of thiamine deficiency are also common occurrences in ICU patients (see Table 48.4), and include: (*a*) a cardiomyopathy, also known as "wet beriberi", (*b*) Wernicke's encephalopathy, (*c*) a peripheral neuropathy, also known as "dry beriberi", and (*d*) lactic acidosis.

CARDIOMYOPATHY: The cardiomyopathy associated with thiamine deficiency may be the result of increased oxidative stress (27), and it typically produces a high output heart failure (28). Thiamine deficiency from chronic furosemide use could also aggravate other forms of cardiomyopathy, although thiamine supplementation in patients with heart failure has no convincing effects on cardiac function or symptomatology (29).

ENCEPHALOPATHY: Wernicke's encephalopathy is the most cited consequence of thiamine deficiency. The clinical presentation is classically described as the combination of mental status changes, ocular abnormalities, and ataxia, but this "triad" occurs in only 20% of cases (30). About 80% of patients have mental status changes (e.g., somnolence, confusion, stupor), and 30% have ocular abnormalities (e.g., nystagmus, lateral gaze paralysis) (30). Magnetic resonance imaging (MRI) can show characteristic abnormalities, like the ones in Figure 48.2, and these may be the only clue to the diagnosis (see later).

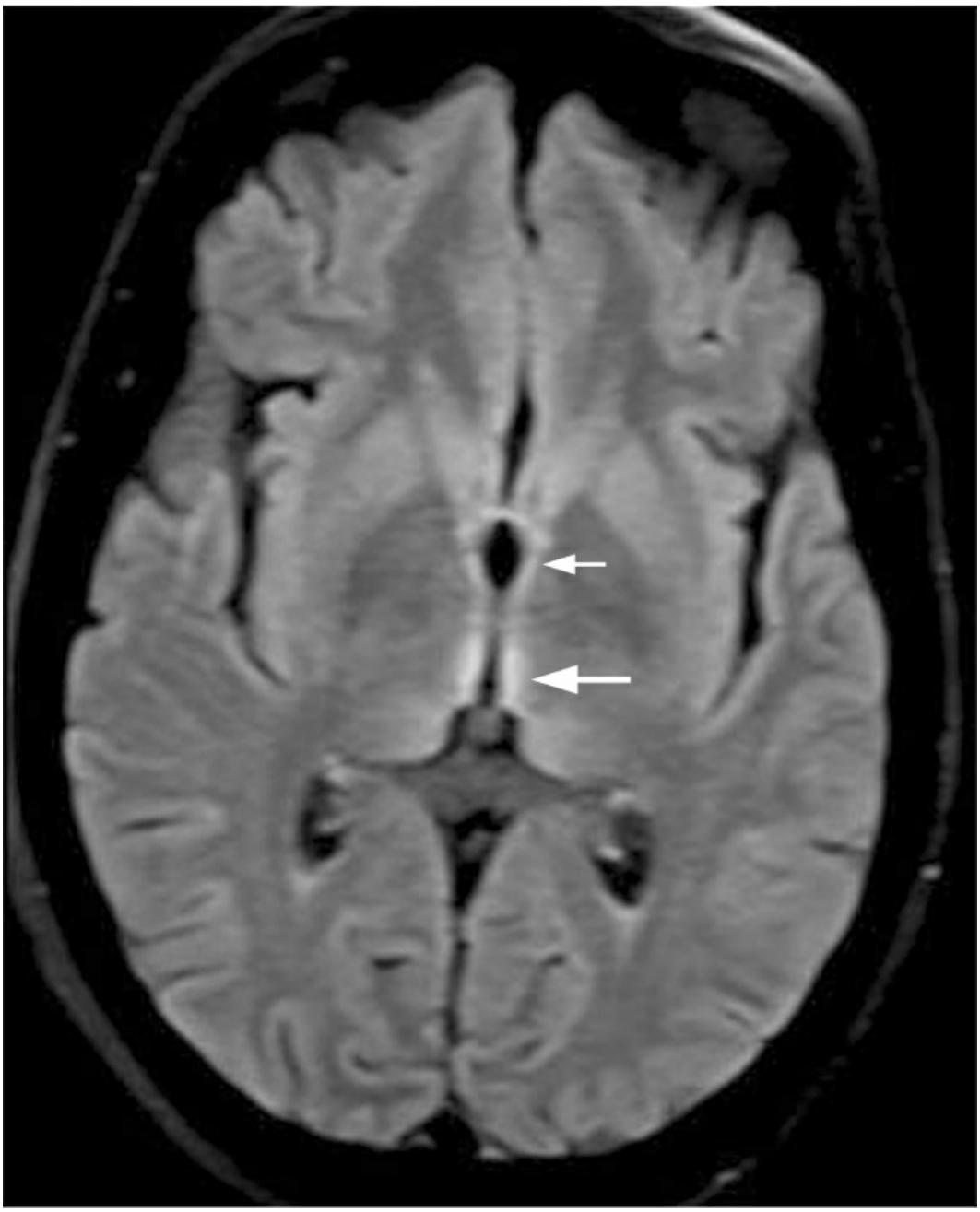

FIGURE 48.2 FLAIR imaging on MRI showing hyperdense signals bilaterally in the medial thalamus (large arrow) and the periventricular region of the third ventricle (small arrow) in a patient with Wernicke's encephalopathy. Case courtesy of Ashutosh Gandhi, Radiopaedia.org, rID: 19865.

LACTIC ACIDOSIS: As explained, thiamine deficiency impairs the movement of pyruvate into mitochondria, and this results in an increase in lactate formation (see Figure 9.5). Thiamine deficiency may be responsible for some of the lactic acidosis associated with sepsis (31), and for the lactate elevation in diabetic ketoacidosis (32). Lactate elevation of unclear etiology should always prompt suspicion of thiamine deficiency.

PERIPHERAL NEUROPATHY: Relatively little is written about the peripheral neuropathy in thiamine deficiency, other than it often coexists with Wernicke's encephalopathy (30).

Diagnosis

The diagnosis of thiamine deficiency is challenging. Plasma thiamine levels are unreliable. Most of the thiamine in the body is present as thiamine pyrophosphate (TPP), which is located predominantly in red blood cells, so a whole blood assay for TPP has some merit for evaluating thiamine status. The normal level is 63–229 nmol/L (30). However, this test is not available in many clinical laboratories, and results are often not immediately available.

Because of the limitations in the laboratory evaluation of thiamine status, thiamine deficiency is considered a clinical diagnosis (30). Unfortunately, the manifestations of thiamine deficiency are common occurrences in critically ill patients. Thiamine deficiency should be suspected when one of the manifestations (heart failure, encephalopathy, or lactic acidosis) has no apparent etiology, especially in the presence of a predisposing condition (e.g., alcohol abuse).

IMAGING: MRI is considered the most reliable method for confirming the diagnosis of Wernicke's encephalopathy (30). Common abnormalities include an increased T2 signal bilaterally in the medial regions of the thalamus (see Figure 48.2), and in the hypothalamus, mamillary bodies, and midline regions of the cerebellum (30). MRI has a sensitivity of 53% and a specificity of 93% for the diagnosis of Wernicke's encephalopathy (30).

Treatment

Patients who are considered at risk for thiamine deficiency (e.g., alcoholics) are often given *thiamine in a conventional dose of 100 mg daily* (33), but this *is inadequate for correcting thiamine deficiency* (33). The recommended treatment for suspected or confirmed cases of thiamine deficiency is shown in Table 48.4 (33,34). The intravenous route is always preferred for acute thiamine replacement, as thiamine uptake from the GI tract is often erratic in critically ill patients. When replenishing thiamine, it is important to *identify and correct magnesium deficiency*, so the infused thiamine can be utilized (by conversion to thiamine pyrophosphate).

Vitamin D Deficiency

Vitamin D deficiency is reported in 40–100% of ICU patients (35). This is not surprising because the recommended daily requirement for vitamin D is 600 IU for adults (and is likely to be even higher in critically ill patients), yet enteral and parenteral nutrition regimens typically provide only about 200–400 IU of vitamin D daily.

Consequences

The major consequence of vitamin D deficiency is bone health, which should have a relatively minor impact in critically ill patients. However, vitamin D is also involved in regulation of the immune response, and vitamin D deficiency is associated with increased rates of infection in ICU patients (36).

Diagnosis

The diagnosis of vitamin D deficiency is based on the plasma concentration of a vitamin D

metabolite, 25-hydroxyvitamin D (25-OHD). Plasma levels below 50 nmol/L indicate a deficiency state, and plasma levels below 30 nmol/L indicate a severe deficiency (37).

TREATMENT: The reliability of oral vitamin D supplementation in critically ill patients is unclear. A single IM injection of 150,000 IU of cholecalciferol can increase plasma 25-OHD levels to normal in 90% of ICU patients (37).

Antioxidant Vitamins

The following vitamins are considered major endogenous antioxidants that protect tissues against oxidative injury (38).

. *Vitamin E* (α-tocopherol) is the major lipid-soluble antioxidant in the body, and protects all cell membranes from oxidative damage (39).

. *Vitamin C* (ascorbic acid) is a major water-soluble antioxidant, and scavenges (detoxifies) reactive oxygen species. It is also essential for maintaining vitamin E in its active form (40).

Both antioxidant vitamins can be deficient in critically ill patients (41,42) and there is evidence that supplementing vitamin C and vitamin E can improve outcomes (43), although this is not a consistent finding (38). Nevertheless, considering that oxidative stress plays an important role in the pathogenesis of inflammatory-mediated organ injury (44), it seems wise to maintain adequate antioxidant protection in critically ill patients.

ESSENTIAL TRACE ELEMENTS

A trace element is one that is present in amounts less than 50 μg per gram of body tissue (45). Seven trace elements are considered essential in humans (i.e., are associated with deficiency syndromes), and these are listed in Table 48.5 along with the daily requirements for each element in healthy men and women. As mentioned for vitamins, the essential trace element requirements are likely to be higher in critically ill patients. The following trace elements deserve mention because of their relevance to oxidative tissue injury.

Iron

Healthy adults have about 4.5 grams of iron, but very little of this is free, unbound iron (46). Most of the iron in the body is bound to hemoglobin, and the remainder is bound to ferritin in tissues and transferrin in plasma. Circulating transferrin is only 30% saturated with iron, so any increase in iron will be quickly bound by transferrin, thus preventing a rise in free iron in plasma. The paucity of free iron in the body has survival value, because free iron has a pivotal role in oxidative tissue injury (47).

Iron and Oxidative Injury

Iron has two actions that promote oxidative cell injury.

. Iron in its reduced form (Fe^{2+}) is necessary for the production of hydroxyl radicals (see Figure 25.6), which are the most destructive of the reactive oxygen species, capable of damaging all

vital cell components.

. Iron-induced lipid peroxidation can produce a form of regulated cell death known as *ferroptosis* (48). This process is triggered by inflammation, and it is has a major role in inflammatory tissue injury (49).

The risk of harm from free iron would explain why hypoferremia is common in conditions associated with systemic inflammation (50). This risk is also reason to avoid administering iron in critically ill patients unless there is evidence of iron depletion in tissues with resultant anemia. Tissue iron stores can be assessed with the plasma ferritin level; i.e., a ferritin level below 18 µg/L indicates probable iron deficiency, while iron deficiency is unlikely if the ferritin level exceeds 100 µg/L (51).

TABLE 48.5 Daily Requirements for Essential Trace Elements in Adults, Ages 51–70

Element	Men	Women†
Chromium	30 µg/d	20 µg/d
Copper	900 µg/d	900 µg/d
Iodine	150 µg/d	150 µg/d
Iron	8 mg/d	8 mg/d
Manganese	2.3 mg/d	1.8 mg/d
Selenium	55 µg/d	55 µg/d
Zinc	11 mg/d	8 mg/d

From the National Institutes of Health, Office of Dietary Supplements. Available at ods.od.nih.gov/HealthInformation/nutrientrecommendations.aspx. Accessed 7/2/2024. †Does not include pregnant or lactating women.

Selenium

Selenium is an essential cofactor for the enzyme glutathione peroxidase, which is a major source of intracellular antioxidant activity (see Figure 25.7). The daily requirement for selenium is 55 µg in healthy adults (see Table 48.5), but selenium utilization is increased in acute illness (52), and selenium deficiency is common in critically ill patients (45).

Plasma selenium levels can be monitored in patients at risk for oxidative stress (e.g., from systemic inflammation). Plasma levels below 100 µg/L are associated with reduced activity of glutathione peroxidase (53). Selenium supplementation can be given intravenously (as sodium selenite), and the maximum dose considered safe is 225 µg daily (54).

A FINAL WORD

A Fly in the Ointment

The rationale for providing nutrition support in critically ill patients is to prevent or alleviate malnutrition. This is a valid reason if the malnutrition is due to decreased nutrient intake (i.e., starvation), but *the malnutrition associated with critical illnesses is the result of abnormal nutrient processing*, and providing nutrients will not correct this type of malnutrition until the causative illness is corrected, and the metabolic derangements are resolved. In fact, nutrition support can be harmful in this situation (55), as explained next.

An example of abnormal nutrient processing in acute illness is the fate of a glucose load; i.e., less than 5% of glucose is metabolized to lactate in healthy subjects, while as much as 85% of a glucose load can be recovered as lactate in acutely ill patients (56). This is demonstrated in Figure 48.3 (57). In this case, patients undergoing a major surgical procedure were randomized to receive either Ringer's lactate or a 5% dextrose solution as the IV fluid during the procedure. As indicated in the graph, the dextrose infusions (which averaged 200 grams) resulted in an increase in the plasma lactate to abnormally high levels (>2 mmol/L), which did not occur in the patients who received a dextrose-free fluid.

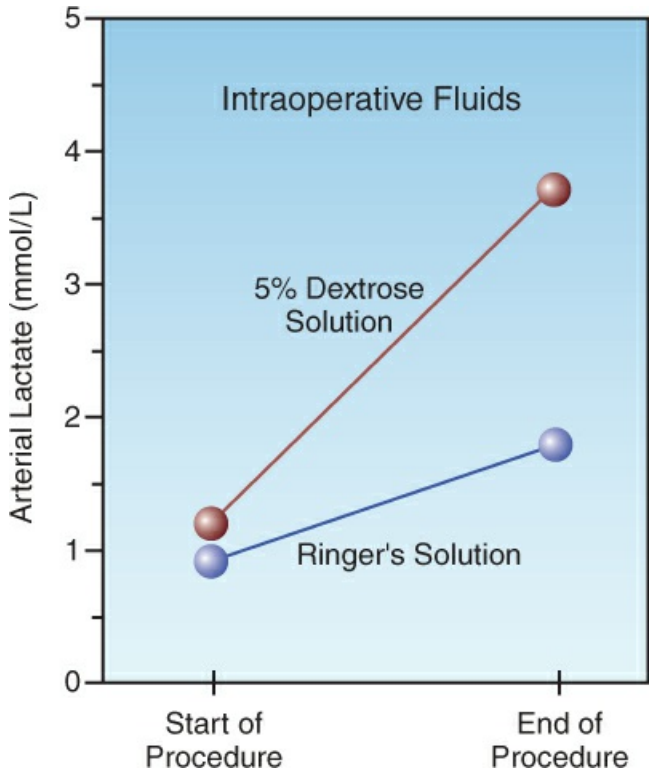

FIGURE 48.3 Influence of dextrose infusions on arterial lactate levels during abdominal aortic surgery. Each data point represents a mean value for patients randomized to receive either Ringer's lactate or a 5% dextrose solution during the procedure. Total volume infused was equivalent with both fluids. Data from Reference 57.

Another potential for "nutrient harm" would be the infusion of lipids in conditions that favor oxidation (e.g. inflammation), because oxidation of the infused lipids can be a source of tissue injury (17), as mentioned earlier.

To summarize, because of the metabolic derangements in critical illness, nutrition support is unlikely to provide the desired nutritional benefit, and can instead be a source of harm. Maybe

this is why we lose our appetite when we get sick?

It seems Hippocrates had the right idea about 2,500 years ago.

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Chapter 49

Enteral Nutrition

Forced feeding . . . goes on because the world still believes it can eat itself well.

Herbert Shelton (*a*)

For patients who are unable to eat, the preferred method of nutrition support is the infusion of liquid feeding formulas into the stomach or small bowel. This not only provides energy from nutrient fuels, it also serves as an *infection control measure* by promoting the barrier function of the bowel mucosa (as explained in the next section).

This chapter presents the practical aspects of providing enteral tube feedings: i.e., when to do it and when not to do it, how to do it, what feeding formulas to use, and what complications to watch for. When possible, recommendations are taken from clinical practice guidelines and recent reviews of the topic (1–5).

GENERAL CONSIDERATIONS

Infectious Risk

The threat of sepsis and organ injury from the bowel is described in Chapter 4. The primacy of this threat is evident in the description of the bowel as "the motor of multiorgan failure" (6). The role of enteral tube feedings in mitigating this threat is summarized in the following statements:

. The presence of bulk nutrients in the lumen of the bowel has a trophic effect on the bowel mucosa that preserves the structural integrity of the mucosa (7). This maintains the barrier function of the bowel mucosa, which protects against invasion from enteric pathogens via *translocation* across the bowel wall (8).

. The trophic influence of enteral nutrition also includes immune defenses in the bowel, such as the production of immunoglobulin A (IgA) by monocytes in the bowel wall, which blocks the attachment of pathogens to the bowel mucosa (9).

. The trophic effect of enteral nutrition requires nutritional bulk rather than the presence of nutrient fuels (i.e., carbohydrates, proteins and lipids), because the oral administration of

parenteral feeding solutions does not produce the effect (10). However, glutamine is believed to be involved in trophism because it is the principal fuel for enterocytes in the bowel mucosa (11).

. The trophic effect of nutritional bulk is lost during periods of bowel rest, which is accompanied by progressive atrophy of the bowel mucosa (6), along with an increased risk of bacterial invasion from the bowel (12).

The sum of these observations indicates that the normal antimicrobial defenses in the bowel are sustained by enteral tube feedings, but not by parenteral nutrition regimens. In this sense, the delivery of enteral tube feedings can be viewed as an infection control measure. This is verified by clinical studies showing *a lower infection rate associated with early institution of enteral tube feedings* (i.e., within 48 hours of admission) (4).

Who and When

The enteral route is always preferred to the intravenous route for nutrition support, and when oral food intake is not possible, *enteral tube feedings should be started within 48 hours of admission* (1–4), unless there is a contraindication to enteral nutrition (see next). *The presence of bowel sounds is not required to initiate enteral tube feedings* (13).

Contraindications

The contraindications to enteral tube feedings are listed in Table 49.1. One concern that receives the most attention is the wisdom of enteral tube feedings in patients with circulatory shock who require a vasoconstrictor drug (a vasopressor) for blood pressure support. The current consensus about this concern is summarized below.

. Enteral feeding is not advised in uncontrolled or progressive circulatory shock.

. Stable or decreasing vasopressor infusions are not a contraindication to enteral nutrition. However, if the infusion rate of norepinephrine is >0.2 µg/kg/min (>14 µg/min in a 70 kg adult), a reduced caloric intake of 10–15 kcal/kg/day (instead of the usual 25 kcal/kg/day) is recommended for the first 7 days, or until the clinical condition improves (14).

TABLE 49.1 Contraindications to Enteral Tube Feedings

1. Uncontrolled circulatory shock
2. Bowel ischemia (suspected or proven)
3. Life-threatening, refractory hypoxemia or hypercapnia
4. Active upper GI hemorrhage
5. Bowel obstruction
6. High-output intestinal fistula
7. Abdominal compartment syndrome
8. Gastric residual volume >500 mL in 6 hours

From Reference 3.

FEEDING FORMULAS

There is a multitude of tube feeding formulas (Abbott Laboratories, the leading source of enteral nutrition formulas in the United States, has 92 different products) (15), but only a small number of formulas are used routinely. The following is a brief description of some characteristic features of feeding formulas. Representative formulas are included in Tables 49.2 and 49.3.

Caloric Density

Feeding formulas are available with caloric densities of 1, 1.2, 1.5, and 2 kcal/mL. Most tube feeding regimens use formulas with a low caloric density (1 or 1.2 kcal/mL), because higher caloric densities have higher osmolalities, which promotes diarrhea. The higher caloric density formulas (1.5 and 2 kcal/mL) are used when fluid restriction is a priority.

TABLE 49.2 Representative Tube Feeding Formulas

Feeding Formula	Caloric Density (kcal/mL)	Protein (g/L)	Fiber (g/L)	Osmolality (mosm/kg H_2O)
Isocal	1.0	35	0	324
Vital 1.0[5]	1.0	40	4	411
Osmolite 1.2	1.2	56	0	360
Osmolite 1.5	1.5	63	0	525
Jevity 1.2	1.2	56	17	450
Twocal HN	2.0	84	5	710

[5]An elemental formula, with hydrolyzed proteins and medium chain triglycerides to facilitate absorption.
All formulas, except Isocal are from the Abbott Nutrition Product Guide (15).

Protein Content

The protein content in standard feeding formulas varies from 35 to 65 g/L. (The daily protein requirement for an ICU patient is about 1.5 g/kg, which is 100 grams/day for a 70 kg adult.) Protein-enriched formulas are often designated by the suffix HN (for “high nitrogen”), and they provide about 20% more protein than the standard formulas (see Twocal HN in Table 49.2).

Most enteral formulas contain intact proteins that are broken down into amino acids in the upper GI tract. These are called *polymeric* formulas. There are also feeding formulas where the protein is already broken down into small peptides (called *semi-elemental* formulas) or individual amino acids (called *elemental* formulas) to facilitate absorption from the bowel. This

also promotes water reabsorption from the bowel, so these formulas can be advantageous in patients with troublesome diarrhea. *Vital 1.0* in Table 49.2 is an elemental formula.

Carbohydrate Content

Carbohydrates (usually polysaccharides) are the major source of calories in feeding formulas, and they provide up to 70% of the total calories.

Fiber

The term "fiber" refers to polysaccharides from plants that are not digested by humans. There are two types of fiber: fermentable, and nonfermentable.

. *Fermentable fiber* is broken down by gut bacteria to produce short-chain fatty acids (butyrate being the most important) that are the principal fuel source for the cells of the colonic mucosa (16). These fatty acids also promote the growth of nonpathogenic bowel microbes (17), which helps to prevent colonization with pathogens. Thus, fermentable fiber promotes the "health" of both the microbiome, and the mucosal barrier in the large bowel.

. *Nonfermentable fiber* is not broken down by gut bacteria, and the undigestible residue creates an osmotic force that draws water into the lumen of the bowel. This increases the water content of stool to facilitate laxation.

The fiber in liquid feeding formulas is a mixture of fermentable and nonfermentable fiber. The feeding formula with the highest fiber content is *Jevity* (see Table 49.2).

Lipid Content

Standard feeding formulas contain polyunsaturated fatty acids (PUFAs) from vegetable oils. The lipid content of feeding formulas typically provides about 30% of the total calories.

Omega-3 Fatty Acids

PUFAs from vegetable oils can serve as precursors for inflammatory mediators (eicosanoids) that are capable of promoting inflammatory cell injury. This concern has prompted the introduction of feeding formulas that contain PUFAs from fish oils (omega-3 fatty acids), which do not promote inflammation. Some of these feeding formulas are shown in Table 49.3. The use of feeding formulas that influence the inflammatory response is known as *immunonutrition* (14).

TABLE 49.3 Immune-Modulating Feeding Formulas

Feeding Formula	Calories (kcal/mL)	ω-3 FAs (g/L)	Arginine (g/L)	Antioxidants
Impact	1.0	1.7	13	Selenium, β-carotene
Optimental	1.0	2.3	6	Vitamins C & E, β-carotene
Oxepa	1.5	4.6	0	Vitamins C & E, β-carotene

ω-3 FAs = omega-3 fatty acids

Fish oil-enriched feeding formulas should not be used routinely (3), but there is some evidence of benefit when they are used in patients with acute respiratory distress syndrome (ARDS) (18). Other conditions that might benefit from immunonutrition are major trauma, and major abdominal surgery (19).

Conditionally Essential Nutrients

Non-essential nutrients can become essential (i.e., require exogenous support) in conditions of increased utilization. Two of these *conditionally essential* nutrients deserve mention.

Arginine

Arginine is a preferred metabolic substrate for injured muscle, and it is also a precursor of nitric oxide (which has a pivotal role in maintenance of peripheral blood flow) (20). Arginine can become depleted in conditions like multisystem trauma, due to increased utilization in skeletal muscle (20). At least 8 enteral feeding formulas contain arginine in concentrations of 8–19 g/L (two of these formulas are included in Table 49.3), although the optimal dose of arginine is not known. Arginine-enriched feedings have a documented benefit (i.e., reduced risk of infection) in the perioperative period for major surgery (21).

RECOMMENDATION: Clinical practice guidelines state that arginine-enriched feedings are a "consideration" in patients with traumatic brain injury, and in perioperative patients in the surgical ICU (2). They should not be used in medical ICU patients, especially those with severe sepsis (because of the risk of hypotension from arginine-initiated production of nitric oxide).

Glutamine

Glutamine is the most abundant free amino acid in the body, and has several functions that have survival value (22). It is a precursor for glutathione, the major intracellular antioxidant, and is essential for nucleic acid synthesis, and for the production of select neurotransmitters (e.g., gamma aminobutyric acid). Glutamine is also an oxidative fuel for cells with a rapid turnover, like the bowel mucosa. Glutamine stores are rapidly depleted in conditions that promote protein catabolism (e.g., sepsis, major trauma, burn injury), and glutamine depletion has a negative impact on outcomes (23).

Glutamine is contained in the proteins provided by tube feeding formulas, but additional

glutamine is recommended in the following conditions (3)

. For critically ill trauma patients, additional glutamine doses of 0.2–0.3 g/kg/day should be added to the tube feedings for the first 5 days of enteral nutrition.
. For patients with burns over more that 20% of the body surface area, additional glutamine doses of 0.3–0.5 g/kg/day should be added to the tube feedings for the first 10–15 days of enteral nutrition.

Glutamine supplementation is not recommended in other conditions.

Carnitine

Carnitine is necessary for the transport of long-chain fatty acids into mitochondria for fatty acid oxidation (24). Carnitine deficiency can be the result of a genetic disorder, malnutrition, hypercatabolic states, and liver failure, and manifestations include hypoglycemia, and a cardiomyopathy (25). A deficiency state is suggested by plasma carnitine levels below 20 mmol/L.

The recommended daily dose of carnitine is 20–30 mg/kg in adults (26). Feeding formulas that provide supplemental carnitine include *Glucerna, Isocal HN, Jevity, and Peptamen*.

Overabundance of Feeding Formulas

Despite the multitude of feeding formulas, there is little evidence that one formula, or one type of formula, produces better outcomes than the others. As a result, there is a limited number of formulas available in each hospital, and you will probably use the same 1 or 2 formulas for most of your patients.

CREATING A FEEDING REGIMEN

This section describes a simple method for creating an enteral feeding regimen. This method is summarized in Table 49.4, and proceeds in four steps.

TABLE 49.4 Creating an Enteral Feeding Regimen

Step 1a. Determine the resting energy expenditure (REE).

Measure the REE with indirect calorimetry (recommended), or estimate the REE as follows:.

$$\text{REE (kcal/day)} = 25 \times \text{wt (kg)}$$

Step 1b. Estimate the daily protein requirement:

$$\text{Protein (g/day)} = (1.2\text{–}1.6) \times \text{wt (kg)}$$

Step 2. Select the feeding formula.

If possible, use a feeding formula with a caloric density of 1–1.2 kcal/mL.

Step 3. Determine the infusion rate:

$$\text{a. Feeding volume (mL)} = \frac{\text{kcal/day required}}{\text{kcal/mL in feeding formula}}$$

For continuous infusions:

$$\text{b. Infusion rate (mL/hr)} = \frac{\text{Feeding volume (ml)}}{\text{24 (hr)}}$$

Step 4. Adjust the protein intake, if necessary:

a. Determine the projected daily protein intake:

$$\text{Protein In (g/day)} = \text{Feeding volume (L/day)} \times \text{protein (g/L) in formula}$$

b. If the projected intake is less than desired intake, add powdered protein to the feeding solution to correct the discrepancy

Step 1. Determine the daily energy and protein requirements.

The very first consideration is the patient's daily requirement for calories and protein. The daily calorie requirement, also called the *resting energy expenditure* (REE) should be measured using *indirect calorimetry*, which is described in Chapter 48. However, if this is not available, the REE can be estimated using the following simple relationship:

$$\text{REE (kcal/d)} = 25 \times \text{body weight (kg)} \qquad (49.1)$$

The actual body weight is used for this determination, although the dry body weight seems more appropriate. If actual body weight exceeds 125% of ideal body weight, then the "adjusted body weight" can be used for the determination (as shown in Equation [48.3]).

The recommended daily protein requirements in critically ill patients is 1.2 to 2.0 grams/kg/day (1,2). (A median value of 1.6 g/kg/day is appropriate.) When the condition stabilizes, a nitrogen balance can be performed to determine if the protein intake is adequate (as described in Chapter 48). However, this is rarely done while patients are in the ICU.

Step 2. Select a feeding formula.

A standard formula, with 1–1.2 kcal/mL, should be sufficient for most patients. Use formulas with higher caloric densities only if volume restriction is a priority.

Step 3. Calculate the desired infusion rate.

A continuous infusion is recommended for enteral tube feeding (instead of bolus feedings). To determine the desired infusion rate, first calculate the volume of the feeding formula that must be infused to meet the daily caloric requirement, as shown in Table 49.4. The infusion rate (mL/hr) is then the volume to be infused over 24 hours, divided by 24.

Propofol Adjustment

Propofol is a popular agent for short-term sedation during mechanical ventilation, and is delivered in a lipid emulsion that has a caloric density of 1.1 kcal/mL. The calories provided by propofol infusions should be subtracted from the estimated or measured REE to determine the calories that must be provided by the diet. Since propofol provides 1 kcal/mL, the hourly infusion rate of propofol (mL/hr) is equivalent to the hourly caloric yield (kcal/hr).

Step 4. Adjust the protein intake, if necessary.

The final step in the process is determining if the feeding regimen you just created will satisfy the daily protein requirement (from Step 1b). The projected protein intake is simply the daily feeding volume multiplied by the protein concentration in the feeding formula. If the projected protein intake is less than required, powdered protein can be added to the tube feedings to correct the discrepancy.

The Initial Period

The most recent guidelines recommend that *nutrition support should begin at REE levels that are less than the measured or estimated REE* (1,3). This recommendation is based on the discovery that endogenous nutritional adjustments (e.g., gluconeogenesis) are operative in the early stages of acute illness, and adding full nutrition support to these adjustments results in overfeeding (27). In patients who are malnourished at the outset, aggressive early nutrition also increases the risk of the refeeding syndrome (28).

The following recommendations are from the European guidelines for nutrition support (3):

. If indirect calorimetry is used to measure REE, then no more than 70% of the REE should be

provided for the first 3 days of nutrition support. Thereafter, the REE can be gradually increased to 100% over the remainder of the first week.

. If predictive equations are used to estimate REE, then no more than 70% of the REE should be provided for the first 7 days of nutrition support.

FEEDING TUBES

Liquid feeding formulas are delivered into the stomach or duodenum using narrow-bore, flexible nasogastric (NG) tubes like the one shown in Figure 49.1. These tubes are typically 8–10 French in diameter, and 20–40 inches (50–100 cm) in length. They are made of polyurethane, and are much more flexible than the polyvinylchloride NG tubes that are used to decompress the stomach. Because of their flexibility, a guidewire or stylet is necessary for placement.

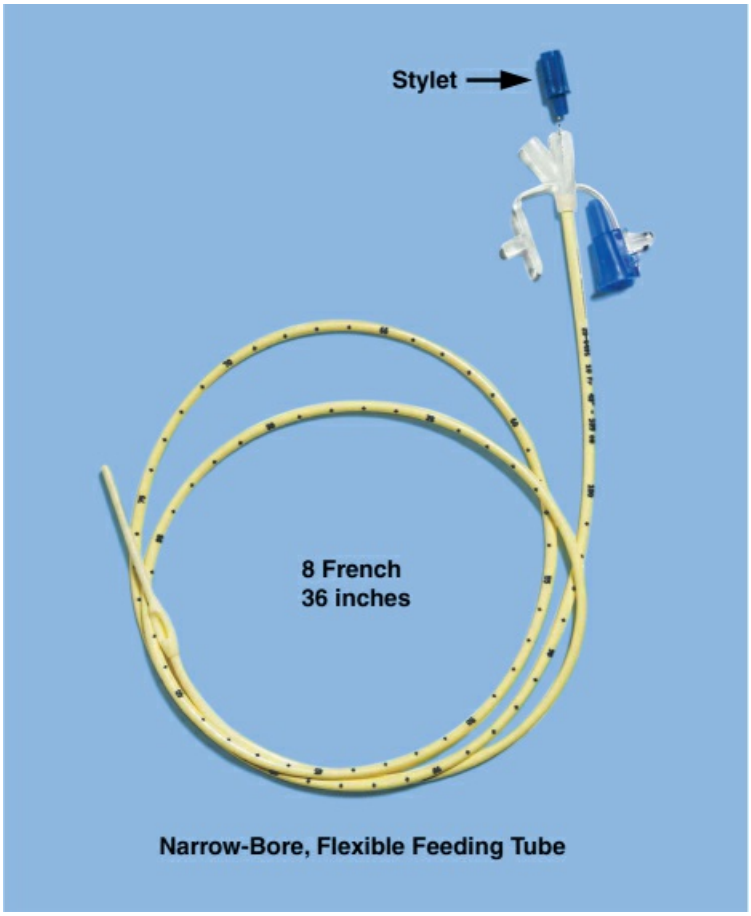

FIGURE 49.1 A narrow-bore, flexible feeding tube with a stylet to facilitate tube placement.

Feeding Tube Placement

Feeding into the stomach is recommended, unless there is evidence of regurgitation and aspiration of feeding formula into the lungs (see later). The distance required to reach the stomach can be estimated by measuring the distance from the tip of the nose to the earlobe and then to the xiphoid process. This “NEX” distance is typically 50–60 cm (29).

The major complication of feeding tube insertion is advancement of the tube into the lungs, which occurs in about 1% of insertions (30). Although a relatively uncommon occurrence, misplaced feeding tubes are a significant source of morbidity and even mortality, especially if there is a delay in detection (31). The problem is that critically ill patients often do not cough or show any signs of distress when a feeding tube enters the lungs (which is especially the case in intubated patients who are heavily sedated), so a portable chest x-ray is required after every insertion to determine if the tube is properly placed. *Feedings should not commence until proper tube placement has been verified*.

Chest Radiography

The appearance of a properly placed feeding tube on a portable chest x-ray is shown in Figure 49.2 (31). The tube runs a straight course down the mediastinum, and bisects the angle created by the tracheal bifurcation. This is evidence that the tube is in the esophagus, and not in the lungs. Placement in the stomach is likely if the tip of the tube is below the dome of the left hemidiaphragm. The optimal tip position is about 10 cm below the dome of the hemidiaphragm (32), which is far enough from the gastroesophageal junction to reduce the risk of reflux into the esophagus.

The Whoosh Test

One of the traditional practices for evaluating tube placement is to push air through the feeding tube and listen for a “whoosh” of air with the stethoscope placed in the epigastric region. This is taken as evidence that the tube is in the stomach, but this is not necessarily the case. In fact, the presence of a whoosh sound does not confirm tube placement in the stomach because a jet of air in the lungs can be heard in the epigastrium (32–34). Despite its popularity, *this test can be misleading, and should be abandoned*.

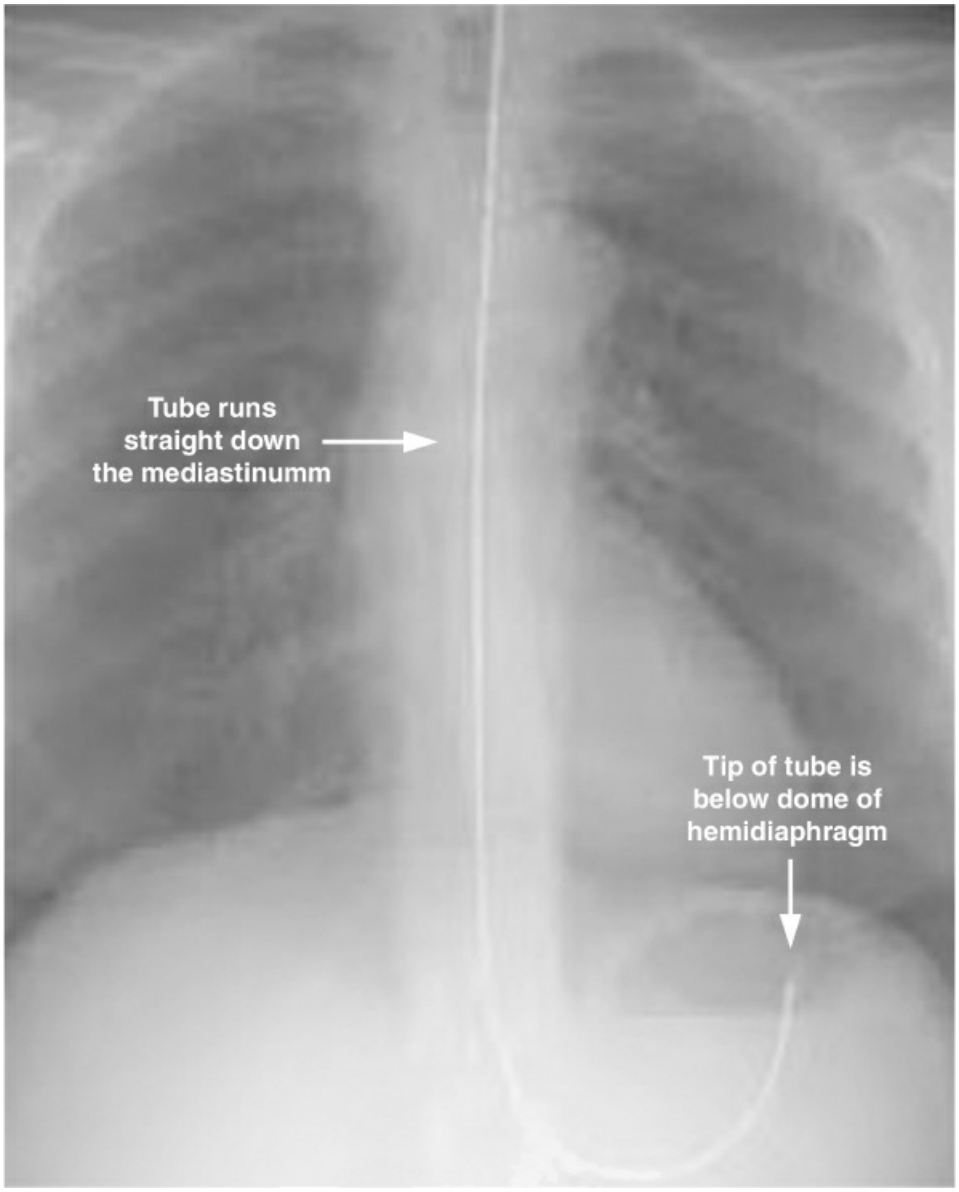

FIGURE 49.2 Portable chest x-ray showing the proper placement of a nasogastric feeding tube. Feedings should not commence until proper placement of the tube is verified radiographically. Image from Reference 31.

Ultrasound

Ultrasound imaging has a sensitivity of 96%, and a specificity of 91%, for confirming the placement of feeding tubes in the stomach (35). However, there is uncertainty about the utility of ultrasound for detecting misplaced feeding tubes, and as a result, ultrasound has not replaced chest radiography for evaluating feeding tube placement.

Misplaced Feeding Tubes

As mentioned earlier, entry of a feeding tube into the airways is usually a covert event, and becomes evident only when the post-procedural chest x-ray looks like the one in Figure 49.3 (36). Note that the tube veers to the right at about the level of the tracheal bifurcation (because it

is following the course of the right mainstem bronchus), in contrast to the straight course of the feeding tube in Figure 49.2. Because they are narrow-bore tubes that are advanced with a rigid stylet, feeding tubes can be advanced far into the lungs, and can break through into the pleural space to produce a pneumothorax (37).

End-Tidal CO_2

Early detection of feeding tubes entering the lungs is possible by monitoring the CO_2 in the infusion port of the feeding tube as it is being advanced. The appearance of a CO_2 waveform, or an increase in PCO_2 to 15 mm Hg, is evidence that the feeding tube has entered the lungs (38). The pooled results of 16 studies has shown that end-tidal CO_2 monitoring has a sensitivity of 96% and a specificity of 99% for the detection of feeding tube misplacement in the lungs (39).

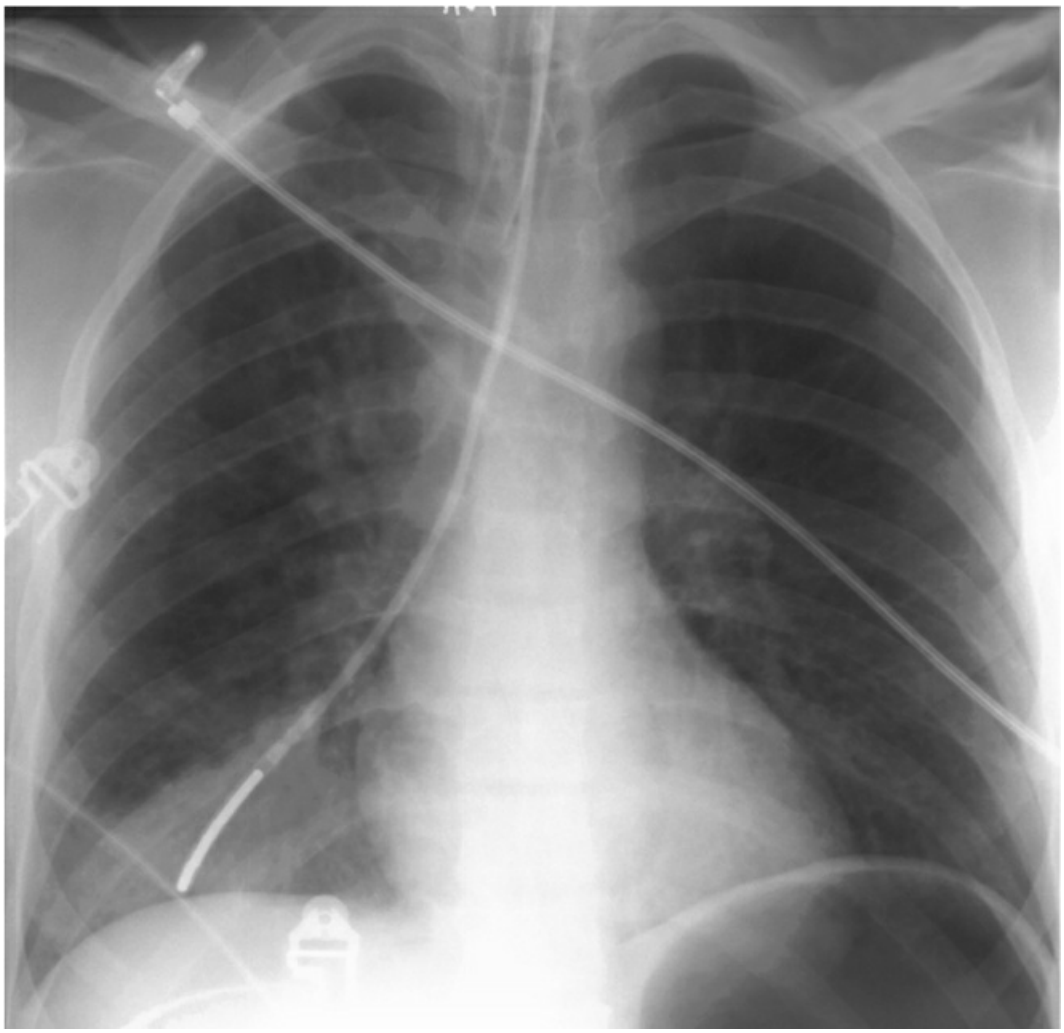

FIGURE 49.3 Portable chest x-ray showing a feeding tube in the right lung. Image from Reference 36, digitally retouched.

End-tidal CO_2 monitoring has one limitation that prevents it from replacing chest radiography: i.e., it does not detect feeding tube misplacement in the esophagus (e.g., from

coiling). However, the early detection of feeding tube entry into the trachea can help to prevent lung injury, and pneumothoraces.

Gastric vs Duodenal Placement

The consensus recommendation is to infuse the liquid feeding formulas into the stomach rather the proximal duodenum. This recommendation is based on studies showing that *there is no difference in the risk of aspiration with gastric versus duodenal feedings* (40,41), and gastric feedings are much easier to deliver. However, duodenal feeding is a consideration in patients with problematic regurgitation and aspiration of gastric feedings.

COMPLICATIONS OF ENTERAL NUTRITION

The most cited complications of enteral tube feeding include (*a*) occlusion of the feeding tubes, (*b*) regurgitation and aspiration of the feeding formula, (*c*) diarrhea, and (*d*) inadequate nutrition support from frequent interruptions of the tube feeding.

Tube Occlusion

Narrow bore feeding tubes can become occluded by protein precipitates that form when acidic gastric secretions reflux into the feeding tubes (42). Standard preventive measures include flushing the feeding tubes with 30 mL of water every 4 hours, and using a 10 mL water flush after medications are instilled.

Restoring Patency

If flow through the feeding tube is sluggish, flushing the tube with warm water can restore flow in 30% of cases (42). If this is ineffective, *pancreatic enzyme* (Viokase) can be used as follows (43):

Regimen: Dissolve 1 tablet of Viokase and 1 tablet of sodium carbonate (324 mg) in 5 mL of water. Inject this mixture into the feeding tube and clamp for 5 minutes. Follow with a warm water flush. This should relieve the obstruction in about 75% of cases (43).

If the feeding tube is completely occluded, attempt to pass a flexible wire through the tube to clear the obstruction. If this is unsuccessful, replace the feeding tube without delay.

Regurgitation/Aspiration

The most feared complication of tube feedings is regurgitation and aspiration of the liquid feedings into the lungs. Microaspiration occurs in almost half of critically ill patients (44), and there is usually no observable feeding solution in the airways. The heightened risk of regurgitation/aspiration is the result of impaired gastric motility and reduced or absent lower esophageal sphincter tone (45,46). Monitoring gastric residual volumes has been used to determine the risk of regurgitation/aspiration, but with limited success.

Gastric Residual Volume

The traditional practice has been to monitor the gastric residual volume (GRV) routinely (e.g., at least once per shift), and interrupt enteral feeding if the GRV exceeds a threshold volume. (This

volume varies from hospital to hospital, but is usually 150–250 mL.) However, there is no convincing evidence that this practice reduces the risk of aspiration, or otherwise influences outcomes (46), but it does result in frequent interruptions of enteral nutrition, and is a common cause of inadequate nutrition support (2).

RECOMMENDATIONS: The consensus recommendations regarding the GRV are as follows (2,3):

. Routine monitoring of GRV is not necessary, but if it is measured (e.g., when aspiration is suspected), a GRV >500 mL in 6 hours is reason to temporarily interrupt the tube feeding.

. If tube feeding is interrupted, the head of the bed should be elevated to at least 30° above horizontal, and a trial or prokinetic therapy is warranted.

. If the problem persists when tube feedings are reinstituted, the feeding site should be advanced (i.e., from stomach to duodenum, or from duodenum to jejunum).

TABLE 49.5 Prokinetic Therapy

Agent	Dosing Regimens and Comments
Erythromycin	Dosing: 100–200 mg IV every 8 hrs for 3 days. Comment: The most effective prokinetic agent, but tachyphylaxis occurs after a few days. Three-day Rx does not affect the resident microbiota.
Metoclopramide	Dosing: 10 mg IV every 8 hrs for 3 days. Comment: Less effective than erythromycin, and its efficacy wanes after a few days.
Enteral Naloxone	Dosing: 8 mg via nasogastric tube every 6 hrs. Comment: Blocks opiate receptors in the bowel without antagonizing the analgesic effects of opiates. Used only for gastric dysmotility related to opiates.

Prokinetic Therapy

The prokinetic agents and recommended dosing regimens are shown in Table 49.5. Prokinetic therapy can produce short-term improvement in indices of gastric motility, but the clinical significance of these effects has been difficult to demonstrate (47). The following information deserves emphasis.

. *Erythromycin* promotes gastric emptying by stimulating motilin receptors in the GI tract (48). It is the most effective prokinetic agent (49), and *is recommended as first-line therapy for gastric dysmotility* (3). The effectiveness of erythromycin wanes over a few days, so no more than 3 days of therapy is recommended. There is no evidence that 3 days of erythromycin has any influence on the resident microbiota.

. Metoclopramide promotes gastric emptying by antagonizing the actions of dopamine in the GI tract. It is less effective than erythromycin (49), and is more effective when given in combination with erythromycin (50). Its effectiveness wanes after a few days, and only three days of treatment is recommended (3).

. Combined therapy with erythromycin and metoclopramide is more effective than treatment with either drug alone (50). However, both drugs prolong the QT interval, and this must be

considered when deciding about combination therapy.

. For gastric dysmotility related to opiates, direct intragastric administration of the opioid antagonist *naloxone* can selectively block opioid receptors in the bowel and promote gastric emptying without antagonizing the analgesic effects of the opiate (51). The clinical experience with oral naloxone is limited.

Diarrhea

Diarrhea is reported in as many as 70% of patients receiving enteral tube feedings (52). The liquid feeding formulas can play a role because they are often hyperosmotic to plasma (see Table 49.2), and thus can pull water into the bowel lumen and promote a watery diarrhea. Other sources of diarrhea are unrelated to the feeding formula, and include antibiotics, *Clostridium difficile* infection, and liquid drug preparations.

Liquid Drug Preparations

Liquid preparations are favored for drug delivery through narrow-bore feeding tubes because there is less risk of obstruction. However, liquid preparations have two features that create a risk for diarrhea: i.e., they can be extremely hyperosmolar (≥3,000 mosm/kg H_2O), and they often contain sorbitol (to improve palatability), a well-known laxative that draws water into the bowel lumen (53). Table 49.6 includes a list of diarrhea-prone liquid preparations that might be used in ICU patients.

Management

The management of diarrhea in the ICU can be challenging because of the multiple potential sources. Tube feeding-related management could include the following: (*a*) choose a feeding formula with a lower osmolality, if possible, (*b*) use an elemental formula that has predigested proteins and lipids, which are easier to move into the bloodstream, and (*c*) avoid the liquid drug preparations in Table 49.6, if possible. Although a fermentable fiber might help (by promoting the health of the mucosa), the fiber-containing feeding formulas are a mixture of fermentable and nonfermentable fiber, which provides no advantage in relieving diarrhea.

TABLE 49.6 Liquid Drug Preparations that Promote Diarrhea

> 3,000 mosm/kg H_2O	Contain Sorbitol
Acetaminophen	Acetaminophen
Dexamathasone	Cimetidine
Ferrous sulfate	Isoniazid
Hydroxyzine	Lithium
Metoclopramide	Metoclopramide
Multivitamins	Theophylline
Potassium chloride	Tetracycline
Sodium phosphate	

From Reference 53.

A FINAL WORD

Eating as an Antimicrobial Defense Mechanism

One of the fundamental tenets in critical care is the primacy of the bowel as a source of sepsis, systemic inflammation, and inflammatory organ injury (see Chapter 4). The principal defender in the bowel is the barrier function of the bowel mucosa, which prevents the hordes of enteric pathogens from gaining entry into the body. (Remember that the alimentary canal is outside the body, like the hole in a donut.) And what keeps this mucosal barrier functional is the presence of bulk nutrients in the bowel lumen. The trophic effect of bulk nutrients on the bowel mucosa means that enteral nutrition has a nonnutritive role in protecting against microbial invasion. Stated another way, *eating can be viewed as an antimicrobial defense mechanism*. Interesting concept.

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Chapter 50

Parenteral Nutrition

To lengthen thy life, lessen thy meals.

Benjamin Franklin (*a*)

The intravenous route is used for nutrition support when the enteral route is not feasible, or is unable to provide full nutrition support. This chapter describes the basic features of "parenteral nutrition", and demonstrates how to create a parenteral nutrition regimen for individual patients. The most recent clinical practice guidelines and reviews on the subject are included in the bibliography at the end of the chapter (1–4).

SUBSTRATE SOLUTIONS

Dextrose Solutions

Standard nutrition support regimens use carbohydrates to supply approximately 70% of the daily (nonprotein) calorie requirements. The carbohydrate source for total parenteral nutrition (TPN) is dextrose (glucose), which is available in the solutions shown in Table 50.1 Because the energy yield from dextrose is relatively low (see Table 48.1), the dextrose solutions must be concentrated to provide enough calories to satisfy daily requirements. The standard solution is 50% dextrose (D_{50}), which provides 1,700 kcal per liter. Concentrated dextrose solutions have a very high osmolarity which mandates infusion through large, central veins.

TABLE 50.1 Intravenous Dextrose Solutions

Strength	Concentration (g/L)	Energy Yield* (kcal/L)	Osmolarity (mosmol/L)
5% (D_5)	50	70	253
10% (D_{10})	100	340	505
20% (D_{20})	200	680	1,080
40% (D_{40})	400	1,360	2,220

50% (D_{50})	500	1,700	2,525

*Based on an oxidative energy yield of 3.4 kcal/g for dextrose in its hydrated form.

Amino Acid Solutions

Protein is provided as amino acid solutions that contain mixtures of essential and nonessential amino acids. (*Note:* Humans can synthesize 11 of the 20 amino acids that are used to build proteins. The remaining 9 amino acids, which are called *essential amino acids,* must be provided in the diet. These amino acids include histidine, isoleucine, leucine, lysine, methionine, threonine, tryptophan, and valine.)

Standard amino acid solutions (e.g., Travasol®) are balanced mixtures of 50% essential amino acids and 50% nonessential amino acids. For full nutrition support, a 10% amino acid solution will provides 100 grams of protein per liter, or 16.5 grams of nitrogen per liter. Amino acid solutions can be mixed together with the dextrose solutions and lipid emulsions.

Branched-Chain Amino Acids

Amino acid solutions enriched with branched-chain amino acids (isoleucine, leucine, and valine), such as *Aminosyn II*® are designed for the following situations:

. In progressive liver failure, aromatic amino acids (i.e., phenylalanine, tryptophan, tyrosine) have been implicated in the pathogenesis of hepatic encephalopathy. Branched-chain amino acids competitively block the transport of aromatic amino acids across the blood-brain barrier (5), and can thereby reduce the risk of hepatic encephalopathy (6).

. Branched-chain amino acids are metabolized in skeletal muscle, and parenteral formulas enriched with branched-chain amino acids are more likely to achieve a positive nitrogen balance during periods of metabolic stress like trauma or sepsis (7).

However, despite these theoretical benefits, *nutrition formulas enriched with branched-chain amino acids have not improved outcomes in any of the conditions for which they are designed* (6,7).

Lipid Emulsions

Lipids are provided as emulsions composed of submicron droplets of cholesterol, phospholipids, and triglycerides. The triglycerides are derived primarily from soybean oil, and the features of a popular soybean oil emulsion are shown in Table 50.2 (8,9). As indicated, these emulsions are rich in essential fatty acids (linoleic and linolenic acid), which must be provided in the diet, and which can prevent essential fatty acid deficiency when they provide 3–4% of the daily caloric requirement (10).

Lipids have the highest energy content (9 kcal/g) of the nutritional fuels, and lipid emulsions are used to provide about 30% of the daily energy needs. The soybean emulsions are available in 10% and 20% strengths (the percentage refers to grams of triglyceride per 100 mL of solution): the 10% emulsions provide 1 kcal/mL, and the 20% emulsions provide 2 kcal/mL (8). Unlike the hypertonic dextrose solutions, lipid emulsions are roughly isotonic to plasma, and *can be infused through peripheral veins*. This allows lipids to be used as a major source of calories in protein-sparing nutritional regimens, which are delivered via peripheral veins (as described later in the

chapter). However, for full parenteral nutrition support, lipid emulsions are added to the glucose and protein solutions to create a 3-in-1 nutrient admixture.

Newer Lipid Emulsions

The polyunsaturated fatty acids in soybean oil are needed to prevent essential fatty acid deficiency, but they have also been implicated in the adverse effects of nutritional lipids, which include hypertriglyceridemia, inflammatory injury, and lipid overload syndrome (which are described later in the chapter). In an attempt to reduce the risk of these complications, lipid emulsions have been introduced that incorporate less damaging lipids. These newer products are listed below (9).

. *Clinolipid*® is 80% olive oil and 20% soybean oil. Olive oil contains medium-chain triglycerides, which are more readily metabolized, and less likely to promote the lipid overload syndrome (11).

. *Smoflipid*® is a mixture of 30% soybean oil, 30% medium-chain triglycerides, 20% olive oil, and 15% fish oil. The fish oil is rich in omega-3 fatty acids, which are less likely to promote inflammatory injury.

. *Omegaven*® is pure fish oil, which has the benefits of omega-3 fatty acids, but will not prevent essential fatty acid deficiency unless combined with lipids from soybean oil.

The experience with the above products is limited at the present time.

TABLE 50.2 Characteristics of Lipid Emulsions Based on Soybean Oil

Product:	Intralipid®
Composition:	1. 50% is linoleic acid, a ω-6 fatty acid and essential fatty acid. 2. 25 % is oleic acid, a ω-9 fatty acid. 3. 10% is α-linolenic acid, a ω-3 fatty acid and essential fatty acid.
Strength:	10% (10 g/100 mL) and 20% (20 g/100 mL)
Energy Yield:	1 kcal/mL for 10% solution 2 kcal/mL for 20% solution
Osmolarity:	260 mosm/L
Max Dosage:	2.5 g/kg/day (or 12.5 mL/kg/day of 20% Intralipid)
Complications:	Hypertriglyceridemia, inflammation, lipid overload syndrome

ADDITIVES

Commercially available mixtures of electrolytes, vitamins, and trace elements are added directly to the 3-in-1 nutrient admixture.

Electrolytes

There are numerous electrolyte mixtures that are commercially available. Most have a volume of 20 mL, and contain sodium, chloride, potassium, and magnesium. You must check the mixture used at your hospital to determine if additional electrolytes must be added. Most hospitals have special order forms where the desired electrolyte changes can be specified.

Vitamins

Aqueous multivitamin preparations will provide the normal daily requirements for most vitamins (see Table 48.3) (16). The daily vitamin requirements in ICU patients are likely to be higher than normal, which explains why vitamin deficiencies are commonplace in ICU patients (see the section on "Vitamin Requirements" in Chapter 48).

Trace Elements

A variety of trace element additives are available, and one of these is shown in Table 50.3, along with the recommended daily requirement for the included trace elements. Note that the daily requirements for 5 of the 7 trace elements are not satisfied by the dosing in this product. The consequences of this mismatch are not known.

TABLE 50.3 Trace Element Preparation and Daily Requirements

Trace Element	Daily Requirement†	Multi-Trace 5 Concentrated§
Chromium	30 µg	10 µg
Copper	900 µg	1 µg
Iodine	150 µg	—
Iron	8 mg	—
Manganese	2.3 mg	0.5 mg/d
Selenium	55 µg	60
Zinc	11 mg	5

†From the National Institutes of Health, Office of Dietary Supplements. (See legend of Table 48.5 for the website of origin.)

§Product description, America Regent, Inc.

CREATING A TPN REGIMEN

The following is a stepwise approach to creating a standard TPN regimen for an individual patient. The patient in this example will be a 70 kg adult who is not malnourished and has no volume restrictions.

Step 1

The initial task is to determine the daily requirement for calories and protein. This is described in

Chapter 48, and is briefly reviewed here. The daily energy requirement, or resting energy expenditure (REE), can be measured by indirect calorimetry, or it can be estimated using a simple formula: REE = 25 × weight (in kg). The daily protein requirements can be estimated as 1.2–2.0 grams per kg body weight. You can use actual body weight in these estimates as long as actual body weight is not greater than 125% of the ideal weight (see Appendix 2 for ideal body weights). If actual body weight exceeds 125% of ideal body weight, you can use the adjusted body weight (which is derived in Equation 48.3).

For the 70 kg patient, we'll use a daily protein requirement of 1.4 g/kg. Therefore, the daily requirement for calories and protein will be:

$$\text{Calories: } 25 \times 70 = 1{,}750 \text{ kcal/day}$$

$$\text{Protein: } 1.4 \times 70 = 98 \text{ grams/day} \qquad (49.1)$$

Note: If propofol is being infused, you should determine the calories provided by propofol and subtract those calories from the daily caloric requirement. Propofol is infused in a 10% lipid emulsion, which has a caloric density equivalent to 10% Intralipid (1 kcal/mL). Therefore, the hourly infusion rate of propofol (mL/hr) is equivalent to the hourly yield of calories (kcal/hr).

Step 2

The next step is to determine the volume of the amino acid solution needed to meet the daily protein requirement. A 10% amino acid solution has 100 grams of protein per liter, so one liter of the amino acid solution will satisfy the estimated daily protein requirement (i.e., 98 grams/day).

Step 3

The next step is to determine how to deliver the daily caloric requirement, which should be provided as nonprotein calories in the dextrose solution and lipid emulsion. Start with the lipid emulsion. The standard lipid emulsion in many hospital pharmacies is a 20% emulsion, which provides 2 kcal/mL. Therefore, 250 mL of a 20% lipid emulsion will provide 500 kcal. That leaves 1,750 – 500 = 1,250 kcal that must be provided by dextrose. One liter of 50% dextrose provides 1,700 kcal, or 1.7 kcal/mL, so the volume of D_{50} needed to provide 1,250 kcal is 1,250/1.7 = 735 mL.

Therefore, the parenteral nutrition formulation for this example would be an admixture of the following:

1. 1 liter of 10% amino acid solution
2. 250 mL of a 20% lipid emulsion
3. 735 mL of a 50% dextrose solution (D_{50})
4. 30 mL for vitamins, electrolytes, and trace elements

Step 4

The final step is determining the infusion rate of the nutrient admixture. The total volume of the admixture is 2,015 mL, which is infused over 24 hours, so the hourly infusion rate is 2,015/24 = 84 mL/hr. However, in patients who are at risk for the refeeding syndrome (see later), the American Society of Parenteral and Enteral Nutrition recommends starting at 40–50% of the

nutritional goal, and advancing to full nutrition support as allowed by the serum levels of phosphate, potassium, and magnesium (usually 4–7 days) (12). For this example, starting at 50% of the nutritional goal corresponds to an infusion rate of 42 mL/hr.

COMPLICATIONS

The following complications do not include those associated with central venous catheters, which are required for full parenteral nutrition. Catheter-related complications are described in Chapters 2 and 3.

Carbohydrate Complications

Hyperglycemia

Hyperglycemia is common during total parenteral nutrition (TPN): e.g., in one report, blood glucose levels above 200 mg/dL were recorded in 45% of the patients receiving TPN (13). Tight glycemic control is not recommended in critically ill patients because of the risk of hypoglycemia, which has more serious consequences than hyperglycemia (14). The current recommendation for hospitalized patients is *a target range of 140–180 mg/dL for blood glucose* (15).

INSULIN: Insulin is often necessary for glycemic control during TPN, and Table 50.4 shows the variety of biosynthetic insulins that are available (16). A continuous infusion of regular insulin is preferred for critically ill patients (17), and this can often be accomplished by adding regular insulin to the feeding admixture, and using subcutaneous insulin (lispro) as needed for glycemic control. When patients are clinically stable, half of the daily insulin requirement can be converted to long-acting glargine insulin, which is given once daily.

TABLE 50.4 Insulin Preparations

Type	Name	Onset*	Peak	Duration
Rapid-Acting	Aspart	10–20 min	1–3 hr	3–5 hr
Rapid-Acting	Glulisine	25 min	45–50 min	4–5 hr
Rapid-Acting	Lispro	15–30 min	0.5–2.5 hr	3–6 hr
Short-Acting	Regular	30–60 min	1–5 hr	6–10 hr
Intermediate	NPH	1–2 hr	6–14 hr	16–24 hr
Long-Acting	Glargine	1 hr	2–20 hr	24 hr

*Onset after subcutaneous injection. From Reference 17.

Hypophosphatemia

The movement of glucose into cells is associated with a similar movement of phosphate into cells, which provides phosphate for cofactors (e.g., thiamine pyrophosphate) that participate in glucose metabolism. This intracellular shift of phosphate can result in progressive hypophosphatemia, as shown in Figure 38.2 (18). *Glucose-induced hypophosphatemia is a major component of the refeeding syndrome* (see later), and this mandates attention to monitoring serum phosphate levels when TPN is initiated.

Hypokalemia

Glucose movement into cells is also accompanied by an intracellular shift of K^+ (which is the basis for the use of glucose and insulin to treat severe hyperkalemia). This effect is usually transient, but continued glucose loading during TPN can lead to persistent hypokalemia. Glucose-induced hypokalemia is another component of the refeeding syndrome (see later).

Hypercapnia

Overfeeding promotes CO_2 retention in patients with respiratory insufficiency (19). This has been attributed to glucose metabolism, which produces more CO_2 than protein or lipid metabolism (i.e., glucose has a higher RQ than proteins or lipids, as shown in Table 48.1). However, CO_2 retention appears to be a consequence of overfeeding, and not just overfeeding with carbohydrates (19).

Lipid Complications

Lipid emulsions have the potential for several deleterious effects, including hypertriglyceridemia, inflammatory injury, hepatic steatosis, and the lipid overload syndrome.

Inflammatory Injury

The soybean oil used in standard lipid emulsions is rich in omega-6 and omega-9 polyunsaturated fatty acids that serve as precursors to the formation of eicosanoids (prostaglandins and leukotrienes), which have a pivotal role in the inflammatory response (4,9). The inflammatory potential of soybean–based lipid emulsions is demonstrated by one of the animal models for the acute respiratory distress syndrome (an inflammatory lung injury) which involves the infusion of oleic acid (an omega-9 fatty acid in soybean oil) into the pulmonary arteries (20). This would explain why lipid infusions in TPN formulations are associated with impaired oxygenation, and can prolong the respiratory failure (21,22). The omega-3 fatty acids in fish oil have anti-inflammatory activity, and some of the newer lipid formulations mentioned earlier (e.g., Smoflipid®) have incorporated fish oils to take advantage of this activity.

Hepatic Steatosis

Fat accumulation in the liver (hepatic steatosis) can occur, but is more common in patients receiving long-term TPN. Contributing factors include the ratio of omega-6 to omega-3 fatty acids in the lipid emulsion, and the content of phytosterols (plant sterols) in lipid emulsions (23). The hepatic steatosis can progress to a chronic hepatitis and even cirrhosis if the TPN is very prolonged (24).

Cholestasis

TPN is also associated with cholestasis, which can lead to acalculous cholecystitis (24). This is attributed to the absence of lipids in the proximal small bowel, which prevents cholecystokinin-mediated contraction of the gallbladder.

Lipid Overload Syndrome

The lipid overload syndrome is an uncommon condition that occurs when the lipid-induced increase in serum triglycerides overwhelms the ability to break down the triglycerides, resulting in a clinical syndrome that can include fever, headache, irritability, respiratory distress, jaundice, pancreatitis, pancytopenia, and coagulopathy (25,26). This is reported more frequently in children, and it can resolve when the lipid infusions are temporarily discontinued (26).

Refeeding Syndrome

The refeeding syndrome was first described in World War II, when aggressive feeding of malnourished prisoners of war and concentration camp victims resulted in considerable morbidity and even mortality.

What is it?

The refeeding syndrome is characterized by the following abnormalities (see Table 50.5): hypophosphatemia, hypokalemia, hypomagnesemia, thiamine deficiency, and renal sodium retention (12). Many of the electrolyte abnormalities, along with the thiamine deficiency, are attributed to the introduction of a glucose load in patients with borderline or depleted stores of potassium, phosphate, magnesium, and thiamine. The sodium retention could be the result of hypoalbuminemia from malnutrition.

The clinical manifestations are a consequence of the electrolyte and vitamin deficiencies, and include generalized weakness (from hypophosphatemia), mental status changes and lactic

acidosis (from thiamine deficiency), tachyarrhythmias (from hypokalemia and hypomagnesemia), and pulmonary edema (from sodium retention) (12).

TABLE 50.5 The Refeeding Syndrome

Mechanisms	Possible Manifestations
Hypophosphatemia	Generalized Weakness
Hypokalemia	Hypotension
Hypomagnesemia	Altered Mentation
Hydroxyzine	Lactic Acidosis
Sodium Retention	Tachyarrhythmias
Multivitamins	Pulmonary Edema
Thiamine Deficiency	

From Reference 12.

Predisposing Conditions

The following conditions have been identified as high-risk for the refeeding syndrome (12): weight loss of 5% in one month, or >10% in 6 months, body mass index (BMI) ≤18.5 kg/m^2, poor nutrient intake for the past 5 days, low baseline levels of serum potassium, phosphate, or magnesium, or any patient with a high risk of malnutrition (e.g., from drug abuse).

Recommendations

The following recommendations are for patients who are high-risk for the refeeding syndrome (12):

. Before nutrition support is started, electrolyte abnormalities should be corrected, and thiamine should be started. The American Society of Parenteral and Enteral Nutrition recommends 100–200 mg thiamine daily (12), but this is inadequate for correcting thiamine deficiency (27), and the replacement protocol in Table 48.4 is more appropriate.

. Nutrition support should be started at 40–50% of the estimated nutritional needs (or 10–15 kcal/kg per day), or glucose infusions can be started at 150 grams daily (which is 300 mL of D_{50}). The nutrition regimen is then slowly advanced over the next 4–7 days, while closely monitoring the serum levels of phosphate, potassium, and magnesium.

PERIPHERAL PARENTERAL NUTRITION

Peripheral parenteral nutrition (PPN) is a truncated form of TPN that can be used to provide nonprotein calories in amounts that will spare the breakdown of proteins to provide energy (i.e., *protein-sparing* nutrition support). PPN can be used as a supplement to enteral feeding, or as a source of calories during brief periods of inadequate nutrition. It is not intended for hypercatabolic or malnourished patients, who need full nutritional support,

The osmolarity of peripheral vein infusates should be kept below 900 mosm/L, with a pH between 7.2 and 7.4, to minimize the risk of vascular damage (28,29). This requires dilute amino acid and dextrose solutions, which limits nutrient intake. However, lipid emulsions are isotonic

to plasma, and lipids can be used to provide a considerable portion of the nonprotein calories in PPN.

Method

A popular regimen for PPN is a mixture of 3% amino acids and 20% dextrose (final concentration of 1.5% amino acids and 10% dextrose), which has an osmolarity of 500 mosm/L. The dextrose will provide 340 kcal/L, so 2.5 L of the mixture will provide 850 kcal. If 250 mL of 20% Intralipid is added to the regimen (adding 500 kcal), the total nonprotein calories will increase to 1,350 kcal/day. This should be close to the nonprotein calorie requirement of an average size, unstressed adult (20 kcal/kg/day).

A FINAL WORD

The final word on parenteral nutrition is . . . *AVOID* . . . whenever possible. For an explanation, see the first section of Chapter 49.

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Chapter 51

Adrenal and Thyroid Dysfunction

Judge a tree from its fruit, not from the leaves.

Euripides

(484–406 BC)

Adrenal and thyroid disorders are rarely the primary reason for admission to an ICU. However, critical illness can influence adrenal and thyroid function, and there is concern that this influence can have a negative impact on outcomes in critically ill patients. This chapter describes the spectrum of adrenal and thyroid disorders that occur in critically ill patients, and how critical illness influences adrenal and thyroid function.

ADRENAL SUPPRESSION IN THE ICU

The adrenal gland plays a major role in the adaptive response to stress. The adrenal cortex releases glucocorticoids and mineralocorticoids that promote glucose availability and maintain extracellular volume, while the adrenal medulla releases catecholamines that support the circulation. Attenuation or loss of this adrenal response leads to hemodynamic instability, volume depletion, and defective energy metabolism (1,2). Adrenal insufficiency can remain silent until the adrenal gland is called on to respond to a physiologic stress. When this occurs, adrenal insufficiency becomes an occult catalyst that speeds the progression of acute, life threatening conditions.

Adrenal Activity

The activity of the adrenal glands is governed by the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland, which, in turn, is governed by the production of corticotrophin-releasing hormone (CRH) in the hypothalamus (see Figure 51.1). Adrenal insufficiency can be the result of suppression at the hypothalamic-pituitary level, or primary suppression of adrenal gland activity.

Cortisol

Cortisol (hydrocortisone) is the major glucocorticoid released by the adrenal cortex. The daily production of cortisol in the normal (unstressed) adult is 15–25 mg/day, and this can increase up to 350 mg/day during periods of maximum physiological stress (3).

PLASMA CORTISOL: About 90% of the cortisol in plasma is bound to corticosteroid-binding globulin (CBG) and albumin, while the remaining 10% is the free or biologically active form (3). The commercial assay for plasma cortisol measures both bound and unbound fractions; i.e., total cortisol. This assay can be misleading in acutely ill patients because plasma levels of CBG fall by as much as 50% during an acute illness (3). Studies of the correlation between free and total cortisol in critically ill patients have shown inconsistent results (1). However, free cortisol levels are not readily available, so total cortisol levels are recommended for assessing adrenal function (1).

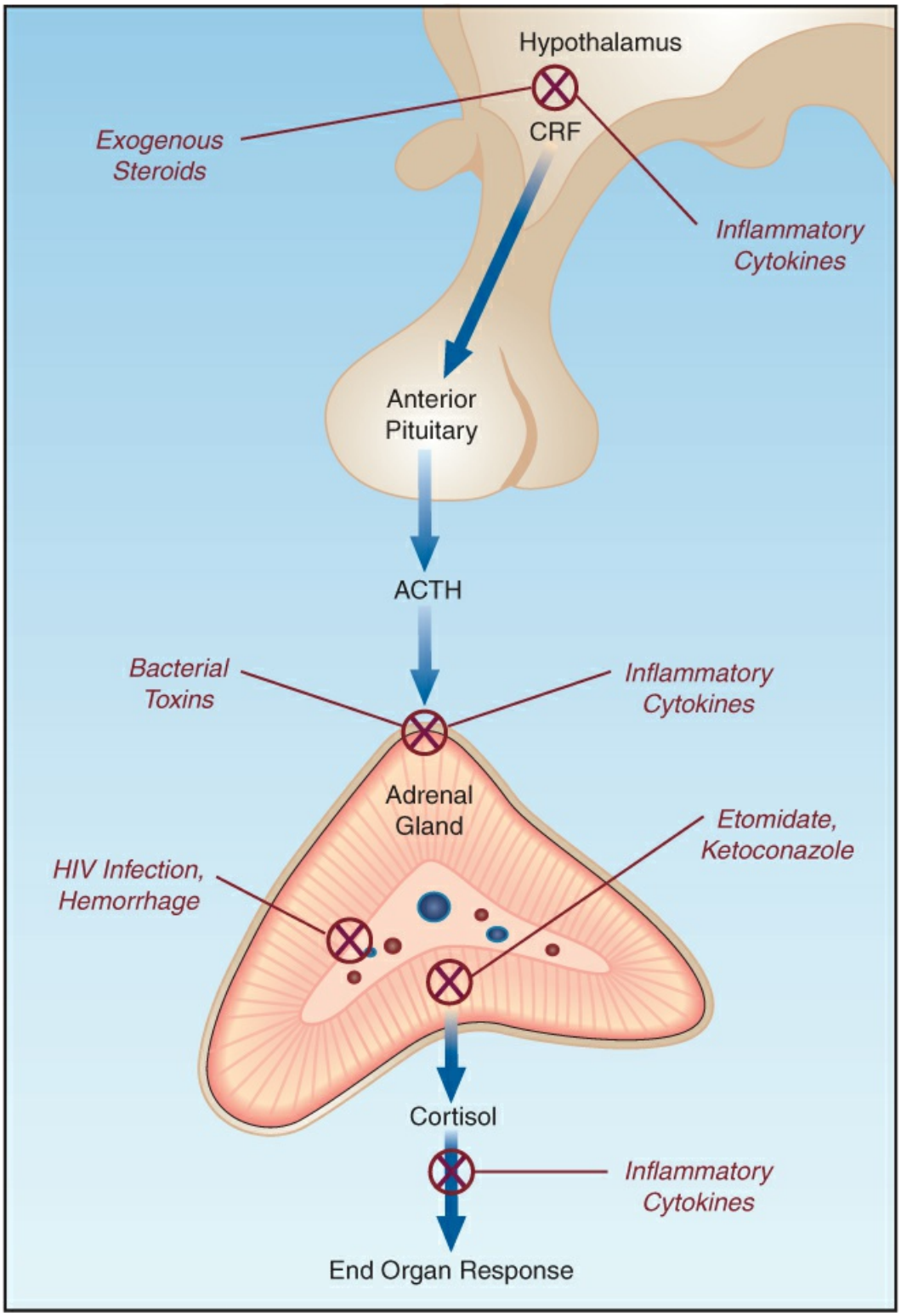

FIGURE 51.1 Mechanisms of adrenal suppression in ICU patients. CRF = corticotrophin-releasing hormone, ACTH = adrenocorticotrophic hormone.

Critically Ill Patients

Adrenal insufficiency is common in critically ill patients. The overall incidence is 10–20% (4), but rates as high as 60% have been reported in patients with severe sepsis and septic shock (5). The adrenal suppression in critically ill patients is *often reversible*, and is called *critical illness-related corticosteroid insufficiency* (CIRCI) (1,3). The mechanisms involved in CIRCI are complex, and not fully elucidated; Figure 51.1 shows some of the known mechanisms (3–6). As indicated, the systemic inflammatory response plays a major role in CIRCI. *Suppression at the hypothalamic-pituitary level* is particularly prominent, and *is responsible for as many as 75% of the cases of adrenal suppression in patients with severe sepsis and septic shock* (5).

Predisposing Conditions

Severe sepsis and septic shock are the leading causes of adrenal suppression in critically ill patients. Specific infectious causes of adrenal suppression include HIV infection, systemic fungal infections, and meningococcemia (which can result in adrenal hemorrhage) (3,6).

Noninfectious sources of adrenal suppression in ICU patients include: (*a*) abrupt discontinuation of chronic steroid therapy, (*b*) adrenal hemorrhage from disseminated intravascular coagulation (DIC) or anticoagulant therapy, and (*c*) drugs that inhibit the synthesis of cortisol (e.g., etomidate and ketoconazole) or accelerate the metabolism of cortisol (e.g., phenytoin or rifampin) (3,6).

Clinical Manifestations

The principal manifestation of adrenal suppression in critically ill patients is *hypotension that is refractory to volume resuscitation* (3–5). The typical electrolyte abnormalities that accompany chronic adrenal insufficiency (i.e., hyponatremia and hyperkalemia), are uncommon in the adrenal suppression associated with critical illness.

Diagnosis

Adrenal suppression should be suspected in any ICU patient with labile blood pressure, or with hypotension of unclear etiology that does not respond to volume resuscitation.

Rapid ACTH Stimulation Test

A popular (but often unnecessary) test of adrenal function in ICU patients is the rapid ACTH stimulation test. This test can be performed at any time of the day or night. A blood sample is obtained for a baseline (random) plasma cortisol level, and the patient is given synthetic ACTH (Cosyntropin) intravenously in a dose of 250 µg. Sixty minutes after the ACTH injection, a second blood sample is obtained for a repeat plasma cortisol level. The interpretation of the test results is described next.

Diagnostic Criteria

Unfortunately, the diagnosis of adrenal suppression in critically ill patients is steeped in uncertainty. The following recommendations represent the current consensus opinion on the subject (1).

. The best predictor of adrenal suppression in critically ill patients is a random plasma cortisol level <10 µg/dL, *or* an increment in plasma cortisol of <9 µg/dL after the intravenous injection

of synthetic ACTH (250 µg).

. In patients with septic shock, plasma cortisol levels are not necessary for identifying patients who might benefit from corticosteroid therapy. In these patients, a trial of intravenous hydrocortisone is recommended when hypotension is refractory to volume resuscitation and moderate doses of a vasopressor agent (1).

The popular approach is to forego the rapid ACTH stimulation test and rely on the random plasma cortisol level for the diagnosis of adrenal suppression (except in patients with septic shock). A random plasma cortisol level that is ≥35 µg/dL is evidence of normal or adequate adrenal function, while a baseline cortisol level that is below 10 µg/dL is evidence of adrenal suppression. A rapid ACTH stimulation test can be performed when the random serum cortisol level is indeterminate. However, *a normal response to ACTH (i.e., an increment in serum cortisol of ≥9 µg/dL) does not eliminate the possibility of secondary adrenal suppression from hypothalamic-pituitary dysfunction* (which may be more common than suspected in ICU patients). A plasma ACTH level is needed for the diagnosis of secondary adrenal insufficiency (2), but this is rarely performed in the ICU setting (for unclear reasons).

Treatment

The treatment of critical illness-related adrenal suppression is *intravenous hydrocortisone in a dose of 200–300 mg daily* (i.e., 100 mg every 8 hours) (4). The addition of a mineralocorticoid (i.e., fludrocortisone, 50 µg orally once daily) is considered optional (4), because hydrocortisone has excellent mineralocorticoid activity (see Table 51.1) (7).

TABLE 51.1 Corticosteroid Comparisons

Corticosteroid	Equivalent Doses	Mineralocorticoid Activity†	Anti-Inflammatory Activity†
Hydrocortisone	20 mg	1	4
Prednisone	5 mg	2	3
Methylprednisolone	4 mg	3	2
Dexamethasone	0.75 mg	4	1

†1 = best, 4 = worst. From Reference 7.

Hydrocortisone can be discontinued after satisfactory resolution of the underlying condition. In septic shock, hydrocortisone can be discontinued when vasopressor therapy is no longer necessary, and serum lactate levels have normalized. A gradual taper of the hydrocortisone dose (over at least a few days) is recommended to prevent a rebound increase in proinflammatory mediators (4).

Steroids as Anti-Inflammatory Agents

Regardless of the presence or absence of CIRCI, corticosteroids are used liberally as anti-inflammatory agents in conditions like septic shock, acute respiratory distress syndrome, autoimmune diseases, and severe infections like pneumonias and meningitis. However, the popular steroid for these conditions is methylprednisolone, despite the fact that *dexamethasone is*

the most potent anti-inflammatory corticosteroid (see Table 51.1). The reason for this discrepancy is unclear.

EVALUATION OF THYROID FUNCTION

Laboratory tests of thyroid function can be abnormal in up to 90% of critically ill patients (8). In most cases, the abnormality is a consequence of non-thyroidal (systemic) illness, and is not a sign of pathologic thyroid disease (8,9). This section describes the laboratory evaluation of thyroid function, and explains how to identify non-thyroidal illness as a cause of abnormal thyroid function tests.

Thyroxine (T_4) and Triiodothyronine (T_3)

Thyroxine (T_4) is the principal hormone secreted by the thyroid gland, but the active form is triiodothyronine (T_3), which is formed by deiodination of thyroxine in extrathyroidal tissues. Both T_3 and T_4 are extensively (>99%) bound to plasma proteins (especially thyroxine-binding globulin), and less than 1% of either hormone is present in the free, or biologically active form (10). Because of the potential for alterations in plasma proteins and protein binding in acute illness, free T_4 and T_3 levels are more reliable for assessing thyroid function in ICU patients. Free T_3 levels are not routinely available, so *free T_4 levels are used to evaluate thyroid function in acutely ill patients*.

Thyroid-Stimulating Hormone (TSH)

The plasma level of thyroid-stimulating hormone (TSH) is considered the most reliable test for the evaluation of thyroid illness, as it can distinguish primary from secondary thyroid disorders, and can also identify nonthyroidal influences on thyroid function. The following general rules apply to the interpretation of thyroid function tests:

. In primary thyroidal illness, the plasma TSH will change in the opposite direction to changes in thyroid hormone levels, and in secondary thyroidal illness (due to aberrations in the hypothalamic-pituitary axis), plasma TSH levels will change in the same direction as changes in thyroid hormone levels.

. For nonthyroidal influences on thyroid function tests, TSH levels are usually in the normal range.

Patterns of Abnormal Thyroid Function Tests

Table 51.2 shows the variety of patterns of free T_4 and TSH levels that can occur with abnormal thyroid function. These patterns will be explained in the following sections on hyperthyroidism and hypothyroidism.

TABLE 51.2 Patterns of Abnormal Thyroid Function Tests

Condition	Free T_4	TSH

Normal Range	0.8–1.8 ng/dL	0.3–4.5 mU/mL
Primary Hyperthyroidism	↑	↓
T_3-Toxicosis	NL	↓
Euthyroid Hyperthyroxinemia	↑	NL
Primary Hypothyroidism	↓	↑
Secondary Hypothyroidism	↓	↓
Euthyroid Sick	↓	NL

NL = normal.

THYROTOXICOSIS

Thyrotoxicosis is almost always the result of primary hyperthyroidism, and the most common cause is autoimmune thyroiditis (Graves disease) (11,12).

Clinical Manifestations

The principal manifestations of thyrotoxicosis include agitation, heat intolerance, tachycardia (including atrial fibrillation), and fine tremors. *Elderly patients with hyperthyroidism can be lethargic* rather than agitated; this condition is called *apathetic thyrotoxicosis*. The combination of lethargy and atrial fibrillation is a frequently cited presentation for apathetic thyrotoxicosis in the elderly (13).

Thyroid Storm

An uncommon but severe form of hyperthyroidism known as *thyroid storm* can be precipitated by acute illness or surgery. This condition is characterized by hyperpyrexia (body temperatures can exceed 104° F), severe agitation or delirium, and severe tachycardia with high output heart failure. Advanced cases are associated with obtundation or coma, generalized seizures, and hemodynamic instability. The mortality rate in this condition is as high as 25%, even with treatment (11).

Diagnosis

The plasma TSH assay is the most sensitive and specific diagnostic test for hyperthyroidism, and is recommended as the initial screening test for suspected hyperthyroidism (11). TSH levels are almost undetectable (<0.01 mU/dL) in most cases of primary hyperthyroidism, and a normal TSH level excludes the diagnosis of hyperthyroidism (11). The free T_4 level is typically elevated in cases of overt hyperthyroidism.

T_3-Toxicosis

In mild or subclinical hyperthyroidism, the plasma TSH level is low, but the free T_4 level can be normal. This condition is sometimes called *T_3-toxicosis*, even though T_3 levels can also be normal (11).

Euthyroid Hyperthyroxinemia

Drugs that block the conversion of T_4 to T_3, such as amiodarone (14) and amphetamines (15) can produce a condition called *euthyroid hyperthyroxinemia* where free T_4 levels are elevated, but TSH levels are normal (11). Heparin therapy can also produce this condition by activating lipoprotein lipase, which increases free fatty acids that will displace T_4 from its binding proteins (11).

Management

The drugs used to treat thyrotoxicosis and thyroid storm are presented in Tables 51.3 and 51.4.

β-Receptor Antagonists

Treatment with β-receptor antagonists relieves the tachycardia, agitation, and fine tremors in thyrotoxicosis. *Propranolol* has been the most widely used β-receptor antagonist in hyperthyroidism (see Table 51.3 for the dosing recommendations), and is preferred in thyroid storm because it blocks the conversion of T_4 to T_3 in high doses (11). However, it is a non-selective β-blocker, which makes it less than ideal for patients with asthma or systolic heart failure. More selective β-blockers like *metoprolol* (25–50 mg PO twice or three times daily) can be used for patients with heart failure or a history of asthma. (*Note:* All β-receptor antagonists are contraindicated during acute exacerbations of asthma). Finally, the ultra rapid-acting agent *esmolol* can be given by continuous infusion for rapid control of heart rate.

TABLE 51.3 Beta Blocker Therapy for Thyrotoxicosis and Thyroid Storm

Drug	Dosing Regimens and Comments
Propranolol	Dosing: 10–40 mg PO 3–4 times daily for thyrotoxicosis, and 60–80 mg IV or PO every 4 hrs for thyroid storm. Comment: The preferred β-blocker, because it blocks conversion of T_4 to T_3 in high doses. However, it is a nonselective β-blocker.
Metoprolol	Dosing: 25–50 mg PO 2–3 times daily. Comment: Relative β-1 selectivity, which may be advantageous in patients with heart failure or asthma.†
Esmolol	Dosing: 50–100 μg/kg/min IV by continuous infusion. Comment: Ultra-short acting agent that allows rapid titration of dosage.

†All β-blockers are contraindicated during acute exacerbations of asthma.

Dosing regimens from Reference 11.

Antithyroid Drugs

Two drugs are used to suppress thyroxine production: methimazole and propyl-thiouracil (PTU). Both are given orally. *Methimazole is preferred for the treatment of thyrotoxicosis, while PTU is favored for the treatment of thyroid storm* (11). Uncommon but serious side effects include cholestatic jaundice for methimazole, and fulminant hepatic necrosis plus agranulocytosis for PTU (11). (See Table 51.4 for the dosing regimens for each drug.)

Inorganic Iodine

In severe cases of hyperthyroidism, iodine (which blocks the synthesis and release of T_4) can be added to antithyroid drug therapy. The iodine is given orally as a saturated potassium iodide solution (Lugol's solution). In patients with an iodine allergy, lithium (300 mg orally every 8 hours) can be used as a substitute (16).

Additional Measures in Thyroid Storm

In addition to the above measures, the management of thyroid storm often requires the following measures:

. Aggressive volume resuscitation is often needed to replace fluid losses from vomiting, diarrhea, and heightened insensible fluid loss.

. Thyroid storm can accelerate glucocorticoid metabolism and create a relative adrenal insufficiency. Prophylactic therapy with intravenous hydrocortisone (300 mg IV as a loading dose, followed by 100 mg IV every 8 hours) is recommended (1).

Successful management of thyroid storm also requires treatment of the precipitating event.

TABLE 51.4 Antithyroid Drugs for Thyrotoxicosis and Thyroid Storm

Drug	Dosing Regimens and Comments
Methimazole	Dosing: 10–20 mg PO once daily for thyrotoxicosis, and 60–80 mg PO once daily for thyroid storm. Comment: Blocks synthesis of T_4. Preferred to propylthiouracil for thyrotoxicosis, but not for thyroid storm.
Propylthiouracil	Dosing: 50–150 mg PO TID for thyrotoxicosis, or 500–1,000 mg PO loading dose, then 250 mg PO every 4 hours for thyroid storm. Comment: Blocks both T_4 synthesis and the conversion of T_4 to T_3. Preferred to methimazole for thyroid storm.
Iodine	Dosing: 5 drops of saturated potassium iodide (Lugol's) solution (250 mg iodine) PO every 6 hrs, for severe thyrotoxicosis or thyroid storm. Comment: Blocks synthesis and secretion of T_4. Used in combination with antithyroid drugs.
Hydrocortisone	Dosing: 300 mg IV as a loading dose, then 100 mg IV every 8 hrs. For thyroid storm only. Comment: Prophylaxis for the relative adrenal insufficiency in thyroid storm. Also blocks conversion of T_4 to T_3 in high doses.

Dosing regimens from Reference 11.

HYPOTHYROIDISM

Symptomatic hypothyroidism is reported in 3–7% of the general population in the United States (17). Most cases are the result of chronic autoimmune thyroiditis (Hashimoto's thyroiditis), while less common causes include radioiodine or surgical treatment of hyperthyroidism, hypothalamic-pituitary dysfunction from tumors and hemorrhagic necrosis (Sheehan's

syndrome), and drugs (lithium, amiodarone, tetracyclines, and antineoplastic agents).

Clinical Manifestations

The clinical manifestations of hypothyroidism are often subtle, and include dry skin, fatigue, muscle cramps, and constipation. Contrary to popular perception, obesity is not a consequence of hypothyroidism (18). More advanced cases can be accompanied by hyponatremia and a skeletal muscle myopathy, with elevations in creatine phosphokinase (CPK), and an increase in the serum creatinine (from creatine released by skeletal muscle) in the absence of renal dysfunction (19).

Cardiovascular

Hypothyroidism can be a source of diastolic heart failure (from impaired relaxation during diastole) and exudative pericardial effusions (from increased capillary permeability) (20). Hypothyroidism also prolongs the Q-T interval, and increases the risk of torsade de pointes (see Figure 19.9) (20).

Myxedema Coma

The most life-threatening presentation of hypothyroidism is a condition characterized by depressed consciousness, hypothermia, hyponatremia, and cardiovascular instability. This condition is referred to as *myxedema coma*, but this is a misnomer, since neither coma nor myxedema is a feature of this condition (21). (Myxedema is nonpitting edema that is associated with hypothyroidism, and is caused by the intradermal accumulation of glycosaminoglycans.)

Diagnosis

Free T_4 levels are always reduced in hypothyroidism (T_3 levels can be normal), while TSH levels are increased (often above 10 mU/dL) in primary hypothyroidism, and are depressed in hypothyroidism due to hypothalamic-pituitary dysfunction (17,18).

Euthyroid Sick

Acute, non-thyroidal illness is associated with low plasma levels of free T_3, which is the result of impaired conversion of T_4 to T_3 in non-thyroidal tissue (8). With increasing severity of illness, both free T_3 and free T_4 levels are depressed, which is the pattern reported in 30–50% of ICU patients (9,10). This condition has also been called the *euthyroid sick syndrome* (8), and is usually associated with normal TSH levels (see Table 51.2).

Treatment

The treatment for mild to moderate hypothyroidism is *levothyroxine* (T_4), which is started at an oral dose of 1.5–1.8 µg/kg/day (22). Therapy is then advanced while monitoring the plasma TSH level. The optimal dose of levothyroxine is the lowest dose that returns the TSH to within the normal range. The usual dose is 75 to 150 µg/day.

Myxedema Coma

Prompt treatment of myxedema coma is mandatory, although the mortality rate is as high as 60%

(22), even with treatment. The recommended therapy is as follows (23):

. Myxedema coma is often accompanied by adrenal insufficiency, so *hydrocortisone* (100 mg IV every 8 hours) is recommended at the outset, with the first dose given before thyroid replacement begins.

. *Levothyroxine* is started with a slow intravenous bolus of 200 to 400 µg, followed by a maintenance dose of 50 to 100 µg orally per day (or 1.6 µg/kg/day). For IV dosing, use 75% of the oral dose.

. Since the conversion of T_4 to T_3 can be depressed in critically ill patients, therapy with *liothyronine* (T_3) can be added, using an IV loading dose of 5–20 µg, followed by a maintenance dose of 2.5–10 µg IV every 8 hours, which is continued until the patient awakens and stabilizes.

Euthyroid Sick

No treatment is recommended for patients with the euthyroid sick syndrome (23), as these patients are not considered to be clinically hypothyroid.

A FINAL WORD

Much Ado About Not Much

The introduction to this chapter included the concern that critical illness has a deleterious influence on adrenal and thyroid function, and that this influence has a negative impact on clinical outcomes in critically ill patients. The following observations do not support this concern.

. Critical illness-related corticosteroid insufficiency (CIRCI) is common in illnesses like septic shock, but there is no evidence that steroid therapy in these illnesses improves outcomes.

. Critical illness can influence plasma thyroid hormone levels (e.g., euthyroid sick syndrome), but this condition is not considered to be clinically relevant, and does not warrant treatment.

Based on these observations, it seems that the interaction between critical illness and adrenal or thyroid function has little relevance or clinical import. (A tree with little fruit, as Euripides might say.)

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Section XVI

OVERDOSES & POISONS

Poisons and medicine are oftentimes the same substance given with different intents.

Peter Latham (1865)

Chapter 52

Pharmaceutical Drug Overdoses

A desire to take medicine is, perhaps, the great feature which distinguishes man from other animals.

Sir William Osler (*a*)

Prescription drug use in the United States is commonplace, (see Figure 52.1), indicating that man's desire to take drugs may be matched by physicians' desire to prescribe them, and this may explain, at least in part, why deaths from drug overdoses have increased more than 5-fold in the past 20-odd years (from 20,000 deaths in the year 2000, to 108,000 deaths in 2022) (1). This chapter describes some of the more frequent or more problematic pharmaceutical drug overdoses, including intoxications from acetaminophen, benzodiazepines, β-blockers, opioids, and salicylates. You won't have to spend much time in an ICU to encounter one of these overdoses.

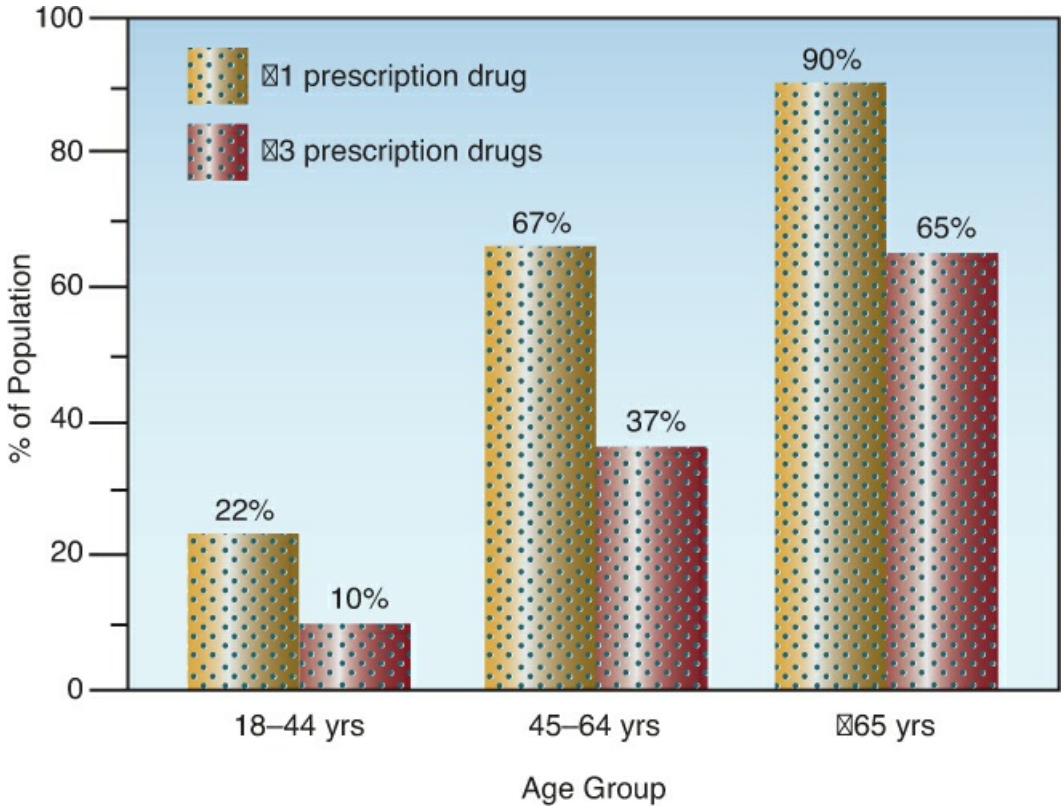

FIGURE 52.1 Prescription drug use in the United States, 2015–2018, by age group. Data from the National Center for Health Statistics, Health United States, 2019: Table 039. Hyattsville, MD, 2019. Available from www.cdc.gov/nchs/hus/data-finder.htm (Accessed 7/16/2024).

ACETAMINOPHEN

Acetaminophen is a ubiquitous, over-the-counter analgesic-antipyretic agent that is included in over 600 commercial drug preparations. It is also a hepatotoxin, and is *the leading cause of acute liver failure in North America, Europe, and Australia* (2). In the United States, acetaminophen is responsible for almost half of the cases of acute liver failure (see Figure 39.1) (3), and about *half of the overdoses are unintentional* (4). In 2011, the U.S. Food and Drug Administration (FDA) issued a mandate for more prominent labeling of the risks of acetaminophen hepatotoxicity, along with a requirement that prescription acetaminophen products be limited to 325 mg per dosage (5). Unfortunately, this mandate has had little impact on the prevalence of acute liver failure from acetaminophen. (See A FINAL WORD for more on this issue.)

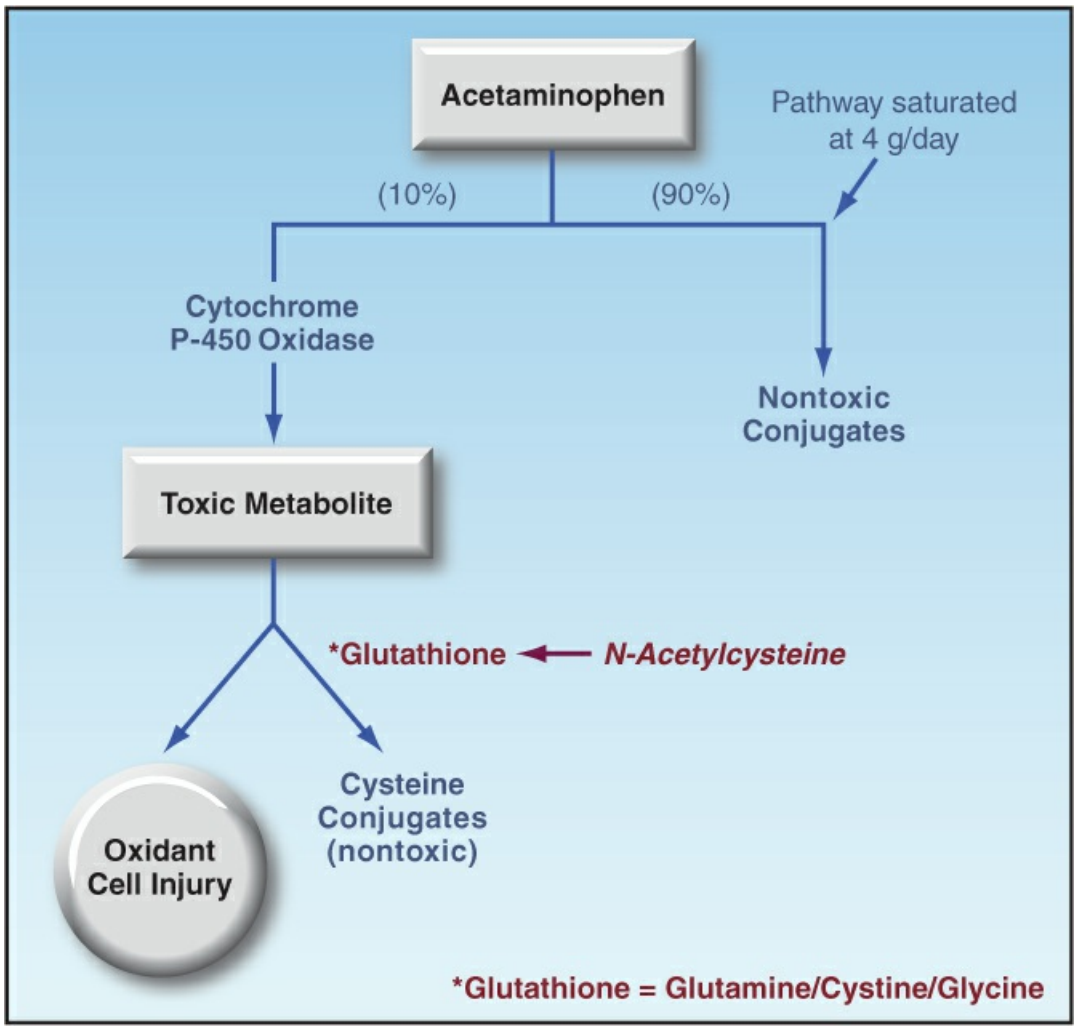

FIGURE 52.2 The hepatic metabolism of acetaminophen. See text for explanation.

Toxic Mechanism

The toxicity of acetaminophen is related to its metabolism in the liver, and the metabolic pathways are shown Figure 52.2. The bulk of acetaminophen metabolism involves the formation of nontoxic sulfate and glucuronide conjugates, which are excreted in the urine. About 10% of the metabolism involves the oxidation of acetaminophen by a cytochrome P450 oxidase group of enzymes to form a toxic metabolite that is capable of lethal cell injury. When the daily dose of acetaminophen is not excessive, the toxic metabolite is removed by conjugation with the cysteine moiety in glutathione, the major intracellular antioxidant. (*Note:* Glutathione is a tripeptide that is composed of cysteine. glutamine, and glycine.) When the daily dose of acetaminophen is excessive (i.e., above 4 grams/day), the nontoxic conjugation pathway becomes saturated, which diverts acetaminophen metabolism to the pathway with the toxic metabolite. The increased traffic in this pathway begins to deplete glutathione reserves, and when glutathione levels fall by 70%, the toxic acetaminophen metabolite accumulates and causes hepatocellular injury (3).

Toxic Dose

. The toxic dose of acetaminophen can vary in individual patients, but is somewhere between 7.5 and 15 grams daily in most adults (6,7). Many poison control centers use 10 grams as a threshold dose that requires further investigation (8). However, certain conditions can increase the susceptibility to acetaminophen hepatotoxicity (see next section).

. According to the FDA, the maximum dose of acetaminophen that is safe in adults is 4 grams per day (9). However, some clinical practice guidelines recommend that for chronic acetaminophen use, the daily dose should not exceed 3 grams (10).

Predisposing Conditions

The following conditions can increase the risk of liver damage from acetaminophen. In the presence of these conditions, a daily acetaminophen dose of >4 grams should be considered as potentially toxic (8).

. Malnutrition, or prolonged periods of fasting, are recognized risk factors because of the potential for depletion of hepatic glutathione stores.

. Patients with chronic alcohol use disorder are at increased risk of acetaminophen hepatotoxicity, *even when daily acetaminophen doses are below the recommended safe level (i.e., <4 grams daily)* (11). This is likely due to the ability of alcohol to increase the activity of the cytochrome P450 enzyme, plus the possible contribution of glutathione depletion from poor nutrition.

. Patients with chronic liver disease are also considered high risk for acetaminophen hepatotoxicity (8), although the evidence for this is not convincing (12).

. Drugs that stimulate cytochrome P450 activity can increase the risk of liver damage from acetaminophen. These drugs include anticonvulsants (carbamazepine and phenytoin) and antituberculosis drugs (INH and rifampin) (12). Opioids can also increase the risk by competing for the nontoxic conjugation pathway, thereby diverting acetaminophen metabolism toward the production of the toxic metabolite (12).

Clinical Presentation

The clinical presentation of acetaminophen hepatotoxicity can be divided into three stages:

. *Stage 1 (First 24 hours):* Symptoms are absent or nonspecific (e.g., nausea, vomiting, malaise), and there may be no evidence of hepatic injury.

. *Stage 2 (24–72 hours):* Hepatic aminotransferases (aspartate aminotransferase [AST], alanine aminotransferase, [ALT]) begin to rise at 24 hours, and can reach levels of 10,000 IU/L (13). Signs of progressive hepatic injury (e.g., jaundice and prolonged INR) begin to appear, and there may be signs of renal impairment.

. *Stage 3 (72–96 hours):* The hepatic injury peaks at 72–96 hours (12). Hepatic encephalopathy may be evident at this time, along with progressive lactic acidosis and acute, oliguric renal failure. Death from multiorgan failure usually occurs at this time.

Risk Assessment

The evaluation of acetaminophen overdoses must include the following: (*a*) the time and dose

ingested, (*b*) the type of ingestion (acute overdose versus unintentional supratherapeutic dosing), (*c*) the drug preparation (immediate vs. extended release), (*d*) the presence of predisposing conditions, and (*e*) evidence of hepatic injury. If an overdose presents within 24 hours of ingestion of an immediate-release preparation, the plasma acetaminophen level can identify the need for antidotal therapy.

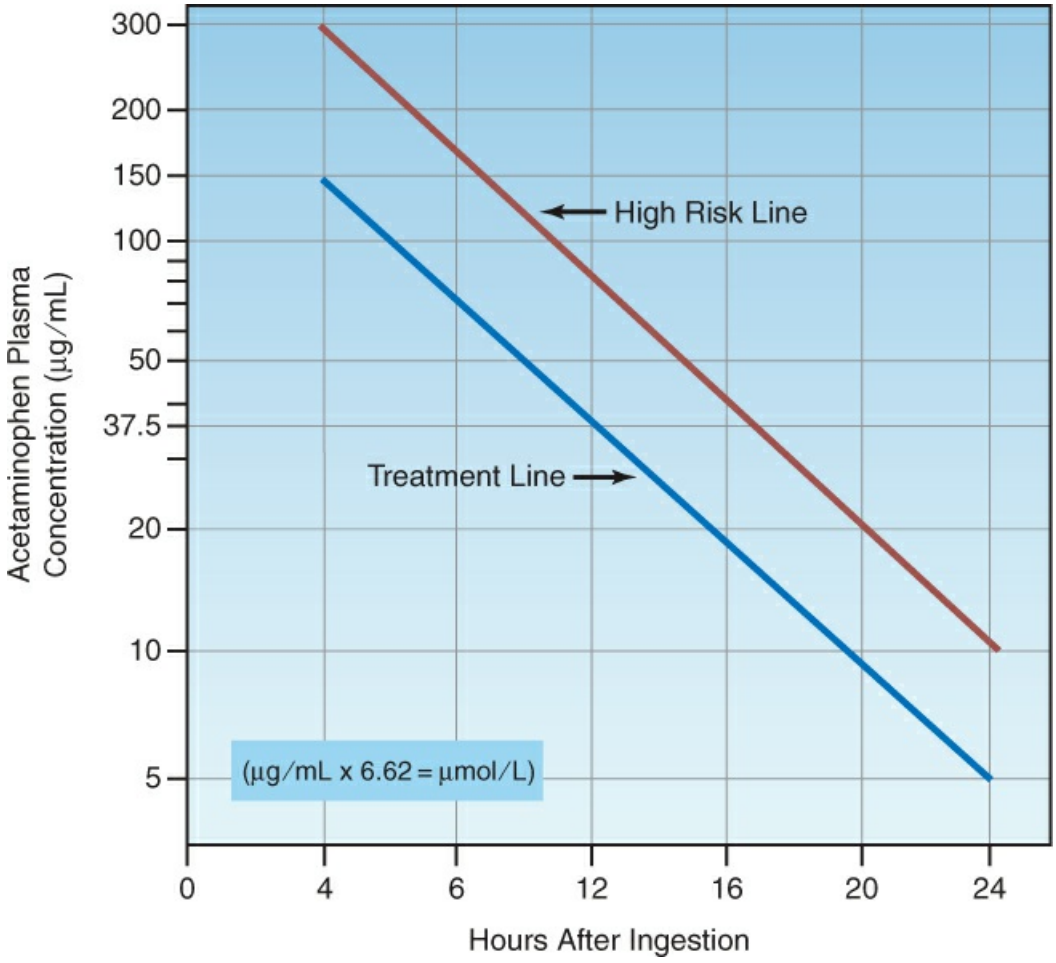

FIGURE 52.3 Nomogram for predicting the risk of hepatotoxicity according to the plasma acetaminophen level between 4 and 24 hours after ingestion. See text for explanation. Nomogram redrawn from Reference 14.

Predictive Nomogram

Plasma acetaminophen levels obtained from 4 to 24 hours after an acute drug ingestion can be used to predict the risk of hepatotoxicity using the nomogram in Figure 52.3 (14). If the plasma level is above the treatment line (which extends from 150 µg/mL at 4 hrs, to 5 µg/mL at 24 hrs), the risk of hepatotoxicity is high enough to warrant antidotal therapy with N-acetylcysteine. If the plasma level is above the high-risk line (from 300 µg/mL at 4 hrs, to 10 µg/mL at 24 hrs), there is a 90% chance of developing hepatotoxicity, and these cases may require extended treatment with N-acetylcysteine (see later).

The predictive nomogram is useful only for acute ingestions that can be accurately timed. If an extended-release preparation was ingested and the plasma acetaminophen level is not above

the treatment line at 4–12 hours after ingestion, a repeat level should be obtained after another 4–6 hours (14). For repeated supratherapeutic ingestions, plasma levels do not predict the risk of hepatotoxicity, and evaluating risk can be challenging.

N-Acetylcysteine

Glutathione does not readily cross cell membranes, so exogenous glutathione is not a viable treatment option for acetaminophen hepatotoxicity. However, glutathione is a tripeptide (i.e., glutamine, cysteine, and glycine), and the cysteine moiety is involved in clearing the toxic acetaminophen metabolite, so a cysteine surrogate, such as N-acetylcysteine (NAC), is a logical (and effective) antidote for acetaminophen hepatotoxicity (see Fig. 52.2).

Treatment with NAC is indicated for any patient with a plasma acetaminophen level above the treatment line in the predictive nomogram. However, *NAC is also recommended for any case of potential acetaminophen hepatotoxicity when the hepatic aminotransferase levels are increased* (14).

Intravenous Regimen

The treatment with NAC can be intravenous or oral. The intravenous route is preferred, and the IV regimen is shown in Table 52.1. The treatment proceeds in two stages (14). The first stage involves a 21-hour infusion of NAC, which is given in 3 separate aliquots, at a total dose of 300 mg/kg (2). This is followed by an evaluation of 4 goals of treatment, which are listed in Table 52.1 as the "NAC stopping criteria". If these goals have not been achieved, the NAC infusion is continued at a dose rate of at least 6.25 mg/kg/hr (14), and the goals are re-evaluated again 12–24 hours later. The NAC infusion is continued until the goals have been achieved.

TABLE 52.1 Intravenous N-Acetylcysteine for Acetaminophen Hepatotoxicity

1. Regimen:

Use 20% NAC (200 mg/mL) for each of the doses below, and infuse in sequence.

1. 150 mg/kg in 200 mL D_5W over 1 hr.
2. 50 mg/kg in 500 mL D_5W over 4 hrs.
3. 100 mg/kg in 1,000 mL D_5W over 16 hrs.

Total Dose: 300 mg/kg over 21 hrs.

2. NAC Stopping Criteria:

1. Plasma acetaminophen <10 μg/mL.
2. AST/ALT normal for patient, or decreased by 25–50%.
3. INR <2.0.
4. Patient feeling well.

a. If NAC stopping criteria are not satisfied, continue IV NAC at a rate of at least 6.25 mg/kg/hr.
b. Recheck criteria every12–24 hrs, and continue NAC until criteria are satisfied.

NAC Regimen from Reference 2; NAC stopping criteria from Reference 14.

Oral Regimen

There is an oral NAC regimen that is as effective as the IV regimen (15), but it is rarely used

because NAC has a very disagreeable taste (due to the sulfur content). The oral regimen is as follows:

. Use 10% NAC, and dilute 2:1 in water to make a 5% solution (50 mg/mL).
. Start with a dose of 140 mg/kg, and follow with a maintenance dose of 70 mg/kg every 4 hours for 72 hours.
. The total dose is 1,330 mg/kg, administered over 72 hours.

There are no clear instructions on checking for improvement or extending the treatment period for oral NAC, as there is for intravenous NAC.

Adverse Reactions

Adverse reactions to intravenous NAC include nausea, vomiting, and cutaneous hypersensitivity reactions (rash, angioedema), which are more common in the first hour (when the NAC dose is the largest), and have a reported incidence that varies from 9% to 77% (16). Other IV regimens have been proposed that reduce the frequency of adverse reactions (2,16), but the efficacy of these regimens is unclear.

Hemodialysis

The elimination of acetaminophen is enhanced by hemodialysis, which is recommended, in addition to NAC, when the plasma acetaminophen concentration exceeds 900 μg/mL, and there is evidence of hepatic encephalopathy (14). During hemodialysis, the intravenous NAC dose should be at least 12.5 mg/kg/hr (because NAC can also be eliminated by dialysis). No dose adjustment is required for the oral NAC regimen.

Outcomes

Most patients respond favorably to NAC, and the reported mortality rate in acetaminophen hepatotoxicity is 0.4% (2). However, an occasional patient will show progressive signs of hepatic injury despite NAC treatment, and these patients should be considered for liver transplantation.

BENZODIAZEPINES

Benzodiazepines are second only to opiates as the drugs most frequently involved in medication-related deaths (17). However, benzodiazepines are rarely fatal when ingested alone (18), and other respiratory depressant drugs (e.g., opiates) are almost always involved in benzodiazepine-related fatalities (17).

Clinical Features

Because overdoses involving benzodiazepines also involve other drugs, the clinical presentation can vary (according to the drugs ingested). Pure benzodiazepine overdoses produce deep sedation but rarely result in coma (18). Respiratory depression (2–12% of cases), bradycardia (1–2% of cases) and hypotension (5–7% of cases) are also uncommon (18). Benzodiazepine intoxication can also produce an agitated confusional state, with hallucinations, that could be

mistaken for alcohol withdrawal (18).

Involvement of benzodiazepines in an apparent overdose can be difficult to establish because there are no serum assays for benzodiazepines, and screening tests for benzodiazepines in urine can miss common agents like lorazepam (19). As a result, benzodiazepine involvement is usually based on the clinical history.

Management

The management of benzodiazepine overdose involves general supportive care, including blood pressure support and mechanical ventilation, if needed. An antidote (flumazenil) is available, but is not popular.

Flumazenil

Flumazenil is a benzodiazepine antagonist that binds to benzodiazepine receptors (GABA-A receptors), but has minimal agonist activity (20). It is effective in reversing benzodiazepine-induced sedation, but is inconsistent in reversing benzodiazepine-induced respiratory depression (21,22).

DOSING REGIMEN: Flumazenil is given as intravenous boluses of 0.2 mg that can be repeated every few minutes to a cumulative dose of 1.0 mg. The response is rapid, with onset in 1–2 minutes, and peak effect at 6–10 minutes (20). The effect lasts about one hour. Since flumazenil has a shorter duration of action than the benzodiazepines, sedation can return after 30–60 minutes. To reduce the risk of re-sedation, the initial dose of flumazenil can be followed by a continuous infusion at 0.3–0.4 mg/hr (23).

ADVERSE REACTIONS: Flumazenil has suffered from reports of frequent adverse effects, as shown in Table 52.2. The data in this table represents the pooled results of 13 clinical trials that compared flumazenil to placebo in patients who presented to an emergency department with impaired consciousness from suspected benzodiazepine overdose (23). As indicated, the minor and major adverse events were significantly more frequent with flumazenil, but the major events (which included seizures) were infrequent, and were significantly different from placebo only at the $p < 0.05$ level. *The issue that is not addressed in these studies is the benefit of awakening with flumazenil.*

TABLE 52.2 Relative Frequencies of Adverse Events with Flumazenil

	Flumazenil	Placebo	p value
Number of Patients	498	492	
Minor Adverse Events†	28%	10%	<0.001
Major Adverse Events§	2.4%	0.4%	0.02

†Most common minor events were agitation, nausea, and vomiting. §Most common major events were supraventricular arrhythmias and seizures. Data from Reference 23.

Because of the risks associated with flumazenil, it is not recommended for patients who present with coma of undetermined etiology, or for patients who have a history of seizures or

chronic benzodiazepine dependence. Its major use at the present time is for rapid awakening following procedural sedation.

B-RECEPTOR ANTAGONISTS

Intentional β-blocker overdoses are uncommon, but can be life-threatening. An effective antidote is available, if needed.

Toxic Manifestations

The typical manifestations of β-blocker overdose are *bradycardia* and *hypotension* (24). The bradycardia is usually sinus in origin, and is well tolerated. The hypotension can be due to peripheral vasodilation (renin blockade), or a decrease in cardiac output (negative inotropic effect), or both.

Membrane Stabilizing Effect

Excessive doses of β-blockers can exert a membrane stabilizing effect that is independent of the β-receptor blockade, and can be life-threatening. The principal consequence is prolonged atrioventricular (AV) conduction, which can progress to complete heart block (25).

Neurotoxicity

Most β-blockers are lipophilic, and have a tendency to accumulate in lipid-rich tissues like the central nervous system, where they can promote *lethargy*, *depressed consciousness*, and *generalized seizures*. The latter manifestation is more prevalent than suspected, and has been reported in 60% of overdoses with propranolol (26). The CNS effects of β-blockers are the result of the membrane stabilizing effect, and not β-receptor blockade.

Glucagon

Glucagon is a regulatory hormone that acts in opposition to insulin by stimulating glycogen breakdown to raise blood glucose levels. In a seemingly unrelated role, glucagon antagonizes the cardiac depression produced by β-receptor antagonists.

Mechanism of Action

The illustration in Figure 52.4 shows how glucagon can correct the cardiac depression caused by β-blockers and calcium channel blockers. The glucagon receptor and β-receptor are linked to the adenyl cyclase enzyme on the inner surface of the cell membrane. Activation of each receptor-enzyme complex results in the hydrolysis of adenosine triphosphate (ATP) and the formation of cyclic adenosine monophosphate (cyclic AMP). The cyclic AMP then activates a protein kinase that promotes the inward movement of calcium through the cell membrane. The influx of calcium promotes interactions between contractile proteins to enhance the strength of cardiac contraction.

The sequence of reactions just described is responsible for the positive inotropic and chronotropic effects of β-receptor stimulation. Since the same reactions occur with activation of the glucagon receptor, *glucagon has cardiostimulatory effects that are not affected by β-receptor*

blockade (27). This allows glucagon to serve as an antidote for β-blocker overdoses.

Clinical Use

Glucagon is indicated for the treatment of hypotension and *symptomatic* bradycardia associated with toxic exposure to β-blockers. When used in the appropriate doses, glucagon will elicit a favorable response in 90% of patients (27). However, *glucagon will not reverse the prolonged AV conduction or neurological abnormalities in β-blocker overdoses* because these effects are not mediated by β-receptor blockade.

CALCIUM ANTAGONIST TOXICITY: Glucagon is also capable of antagonizing the effects of calcium channel blockers, as illustrated in Figure 52.4. However, glucagon is less effective in reversing the cardiac depression in calcium channel blocker overdoses.

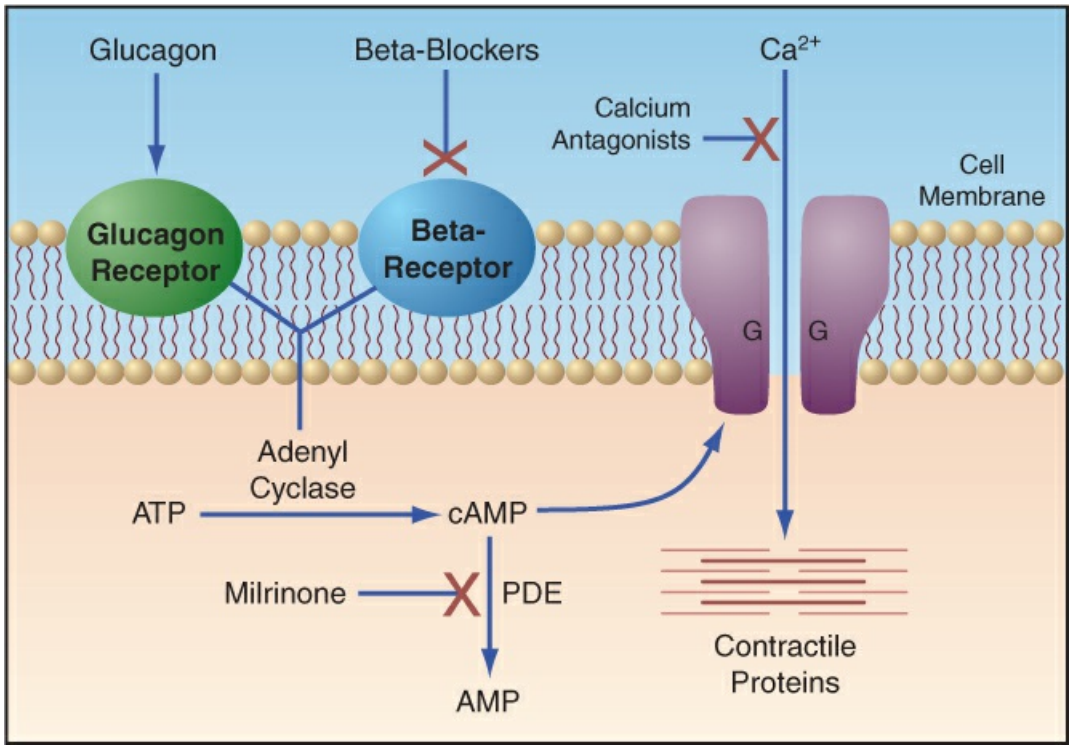

FIGURE 52.4 Mechanisms of drug-induced alterations in cardiac contractile strength. See text for explanation.. Abbreviations: ATP = adenosine triphosphate, cAMP = cyclic adenosine monophosphate, PDE = phosphodiesterase, AMP= adenosine monophosphate.

Dosing Regimen

Dosing recommendations for glucagon are as follows:

. The effective dose of glucagon can vary in individual patients, but *a bolus dose of 3–5 mg IV should be effective in most adults* (26,28). The initial dose is usually 3 mg (or 0.05 mg/kg), and the response should be evident within 3 minutes (29).

. If the response to the initial dose is not satisfactory, a second IV bolus dose of 5 mg (or 0.07 mg/kg) can be given.

. The chronotropic response to glucagon is optimal when the plasma ionized calcium is normal (30).

. The effects of glucagon can be short-lived (5 minutes), and so a favorable response should be followed by a continuous infusion (5 mg/hr).

Adverse Effects

Nausea and vomiting that are refractory to ondansetron are common at glucagon doses above 5 mg/hr (27). Mild hyperglycemia is common, and is the result of glucagon's actions to stimulate glycogenolysis. The insulin response to the hyperglycemia can drive potassium into cells and promote hypokalemia. Finally, glucagon stimulates catecholamine release from the adrenal medulla, and this can cause unwanted increases in blood pressure in patients with hypertension (27).

Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors (e.g., milrinone) augment cardiac contractile strength by inhibiting the breakdown of cyclic AMP, as illustrated in Figure 52.4. These agents can increase cardiac output in the setting of β-blockade (31), and they should add to the increase in cyclic AMP produced by glucagon. However, it is unclear if phosphodiesterase inhibitors add to the effectiveness of glucagon in β-blocker toxicity. Because these drugs are vasodilators, and can produce unwanted decreases in blood pressure, they are generally reserved for the occasional case of β-blocker toxicity that does not respond to glucagon.

OPIOIDS

The problem with opioid overdoses in the United States is certainly no secret, and most cases involve prescription opioids rather than street drugs (32). The adverse effects of opioids are described in Chapter 6, and this section focuses on the use of the narcotic antagonist, naloxone.

Clinical Features

The classic "textbook" description of an opiate overdose is the patient with stupor, pinpoint pupils, and slow breathing (bradypnea), but in reality, it is not possible to identify an opiate overdose based on the clinical presentation or physical examination (33). The response to the narcotic antagonist, naloxone, is probably the most reliable method of identifying an opioid overdose.

Naloxone

Naloxone (Narcan®) is a pure opioid antagonist; i.e., it binds to endogenous opioid receptors, but does not elicit any opioid-like responses. It is most effective in blocking mu (μ) receptors, which are responsible for analgesia, euphoria, and respiratory depression (33). Naloxone can be given by intranasal spray or intravenous injection.

Intranasal Naloxone

The intranasal route is favored for naloxone administration because it is as effective as the

intravenous route (34), but is much easier to administer, and can be given in the field with minimal training.

- Narcan is available as a single-dose nasal spray containing 2 mg or 4 mg naloxone hydrochloride in 0.1 mL of diluent (35). A single dose is delivered into one nostril.
- The recommended dose is either 2 mg or 4 mg, but 2 mg is probably sufficient in most cases, since intranasal doses of 0.4 mg have been effective in clinical studies (34). If there is no response within 3 minutes after the initial dose, a second dose can be given in the other nostril. If the 4 mg dose of naloxone is used, it may be more effective if given in two divided (2 mg) doses in each nostril, as suggested by the plasma naloxone levels in Fig. 52.5 (35).
- The average response time to intranasal naloxone is about 3 minutes (34), and peak blood levels are reached after about 20 minutes (see Fig. 52.5). The elimination half life is between 1.5 and 2 hours (35).
- Intranasal naloxone is effective for reversing both the impaired consciousness and the respiratory depression caused by opioids (34,35). However, the opioid effects are likely to return after 1–2 hours, so a favorable response to naloxone should be followed by a continuous intravenous infusion, at an hourly dose that is two-thirds of the effective dose (diluted in 250 or 500 mL of isotonic saline and infused over 6 hours) (36).

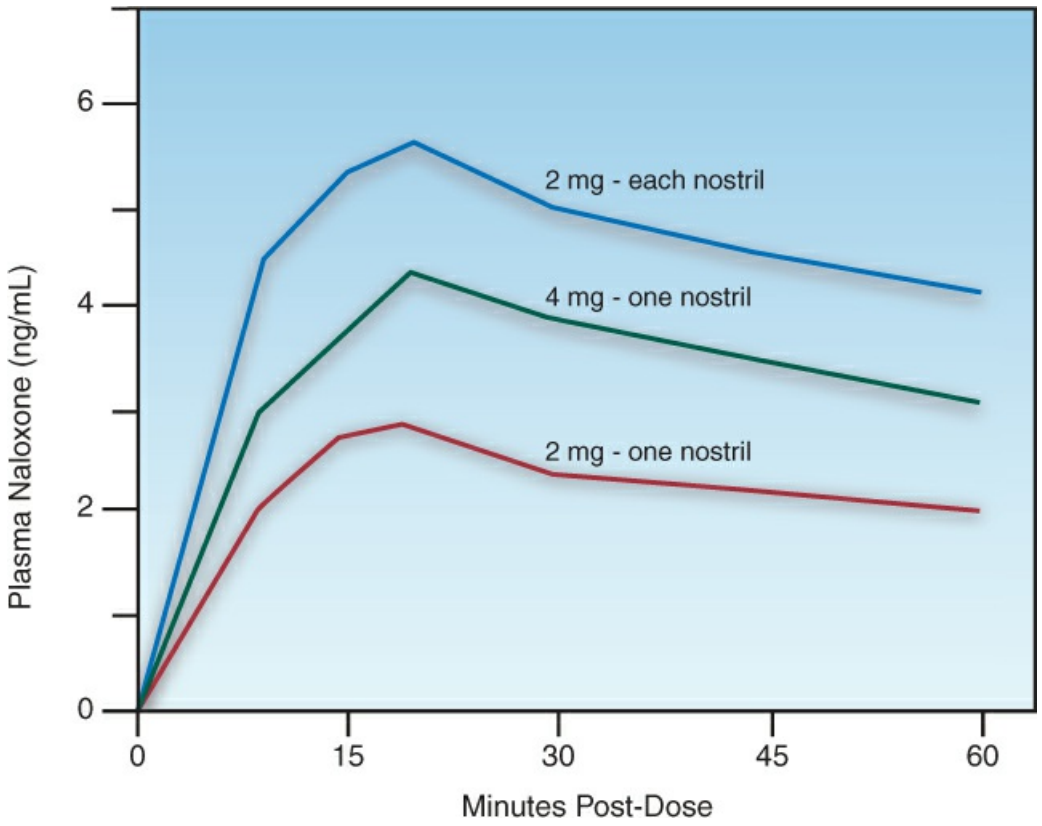

FIGURE 52.5 Plasma naloxone levels after intranasal naloxone in the doses indicated. Note that a dose of 4 mg results in higher plasma levels if the dose is divided, and 2 mg is administered in each nostril. Data from Reference 35.

Intravenous Naloxone

Despite the advantages of intranasal naloxone, intravenous naloxone continues to be the gold standard method for treating opioid overdoses in the hospital setting. The IV route provides greater bioavailability, and a quicker response time, than the intranasal route (34,37) (although the clinical relevance of these differences is unproven). However, the IV route is generally reserved for situations where the nasal spray is not immediately available.

. For patients with a depressed sensorium but no respiratory depression, the initial dose of IV naloxone should be 0.4 mg. This can be repeated in 2 minutes, if necessary. A total dose of 0.8 mg should be effective if the mental status changes are caused by an opioid derivative (38).

. Respiratory depression can be more difficult to reverse than depressed consciousness. The initial naloxone dose for respiratory depression should be 2 mg IV push (33). If there is no response in 2–3 minutes, double the dose to 4 mg. Further doses, if necessary, can be increased to 15 mg. If there is no response to a dose of 15 mg, then opioids are not the cause of the respiratory depression (33).

. The reversal by IV naloxone lasts only about one hour, and opioid effects will return thereafter. Therefore, a favorable response to IV naloxone should be followed by a continuous infusion, using the dosing recommendations described for intranasal naloxone.

Adverse Reactions

Naloxone has few undesirable effects. The most common adverse effect is opioid withdrawal (39). There are also case reports of acute pulmonary edema associated with high-dose naloxone, which is attributed to pulmonary venoconstriction from activation of the sympathetic nervous system (39).

SALICYLATES

Salicylate poisoning receives relatively little attention, but it is second only to acetaminophen poisoning as a cause of suicide-related deaths from over-the-counter analgesics (40). Ingestion of 10–30 grams, or 150 mg/kg, of acetylsalicylic acid (aspirin) can have fatal consequences.

Pathogenesis

Once ingested, acetylsalicylic acid is converted to *salicylic acid*, which is the active form of the drug. Salicylic acid is readily absorbed from the upper GI tract, and metabolism takes place in the liver. *The hallmark of salicylate intoxication is the combination of a respiratory alkalosis and a metabolic acidosis with an elevated anion gap* (41).

Respiratory Alkalosis

Salicylic acid directly stimulates the respiratory centers in the lower brainstem, producing an increase in respiratory rate and tidal volume, and a subsequent decrease in the arterial PCO_2 (i.e., acute respiratory alkalosis). This is one of the earliest signs of salicylate poisoning.

Metabolic Acidosis

Salicylic acid is a weak acid that does not readily dissociate, and thus does not produce a metabolic acidosis. However, salicylic acid uncouples oxidative phosphorylation, which results in a compensatory increase in glycolysis (to generate ATP) and an increase in lactate production. The accumulation of lactic acid (and also ketoacids) results in a high anion-gap metabolic acidosis. This is a relatively late complication, and an acidemic pH is a poor prognostic sign (42).

Other Features

Salicylate-induced uncoupling of oxidative phosphorylation results in an increased metabolic rate, which increases the body temperature and promotes diaphoresis and dehydration.

Clinical Manifestations

The earliest signs of salicylate intoxication are hyperpnea, tinnitus, vertigo, nausea and vomiting, which can appear in the first few hours after a toxic ingestion. These can be followed by agitation and fever, and in severe cases, by coma, cerebral edema, acute respiratory distress syndrome (ARDS), and hemodynamic instability (41). Laboratory studies can reveal hypocapnia and respiratory alkalosis, lactic acidosis, rhabdomyolysis, hypernatremia (from dehydration) and acute kidney injury.

Diagnosis

The plasma salicylate level is used to confirm or exclude the diagnosis of salicylate toxicity.

. The therapeutic plasma salicylate level is 10–30 mg/dL (0.7–2.2 mmol/L).

. Plasma salicylate levels above 40 mg/dL (2.9 mmol/L) are considered toxic, and levels above 75 mg/dL (5.4 mmol/L) are considered life-threatening (41).

. Salicylate levels are often lower in cases of chronic salicylate toxicity.

Management

Management of salicylate toxicity includes general supportive care (e.g., fluids, vasopressors, and mechanical ventilation), plus the following measures.

Activated Charcoal

Because salicylates can slow gastric emptying, and enteric-coated or extended-release aspirin preparations can promote retention of the drug in the gastric lumen, activated charcoal is recommended for all salicylate intoxications, regardless of the time of drug ingestion (41). (However, activated charcoal is most effective if given within 2 hours of drug ingestion.) The dose is 1 g/kg to a maximum dose of 100 grams, which is repeated every 4 hours until the charcoal appears in the stool or the plasma salicylate levels begin to decrease (41).

Alkalinization of the Urine

Alkalinization of the urine increases salicylate excretion, and is one the cornerstones of management for salicylate intoxication. Bicarbonate infusions are used to raise the urine pH using the regimen in Table 52.3 (42,43). This should be continued until the plasma salicylate

levels fall into the therapeutic range.

TABLE 52.3 Protocol for Alkalinization of the Urine

1. Create a bicarbonate solution by adding 3 amps $NaHCO_3$ (44 mEq /amp) to 1 liter D_5W (132 mEq/L). Add 40 mEq KCL.
2. Start with a bicarbonate loading dose of 1–2 mEq/kg.
3. Follow with infusion of the bicarbonate solution at 2–3 mL/kg/hr.
4. Maintain a urine output of 1–2 mL/kg/hr, and a urine pH ≥7.5.

From References 42,43.

HYPOKALEMIA: Bicarbonate infusions will lower the serum potassium (by driving K^+ into cells), and hypokalemia hampers the ability to alkalinize the urine (by increasing the secretion of H^+ into the lumen of the distal tubules). This provides a reason to add K^+ (40 mEq) to the bicarbonate solution, as shown in Table 52.3.

Hemodialysis

Hemodialysis is the most effective method of clearing salicylates from the body (41,44). The indications for hemodialysis include (41): (*a*) a plasma salicylate level >90 mg/dL (>6.5 mmol/L), (*b*) a salicylate level >80 mg/dL (>5.8 mmol/L) plus impaired renal function, or (*c*) evidence of life-threatening intoxication (e.g., cerebral edema, ARDS, multiorgan failure) (41).

A FINAL WORD

Regulating Acetaminophen

If any over-the-counter drug deserves to be regulated, it's acetaminophen. Not only because it is the leading cause of acute liver failure in North America, Europe, and Australia, but also because *half of the overdoses are unintentional* (i.e., the drug ingestion is for therapeutic reasons), indicating a general lack of awareness of the potential for harm with acetaminophen. The FDA issued a mandate for stronger warnings on drug packaging, but who reads that small print? Requiring a prescription that indicates how the drug should be used seems to be the right step for promoting the safe use of acetaminophen.

Acetaminophen gained its popularity in the 1970s because of concerns about the toxicity of aspirin, and it looks like we replaced a potentially toxic drug with a potentially lethal one.

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Chapter 53

Nonpharmaceutical Poisons

It is astonishing with how little reading a doctor can practice medicine, but it is not astonishing how badly he may do it.

Sir William Osler (*a*)

This chapter describes the toxic syndromes produced by exposure to nonpharmaceutical poisons, including carbon monoxide, cyanide, and the toxic alcohols (methanol and ethylene glycol). They are less common than the drug overdoses presented in the last chapter, but they can be lethal if not recognized.

CARBON MONOXIDE

Carbon monoxide (CO) is produced by the incomplete combustion of organic (carbon-based) matter, and is one oxidation reaction shy of carbon dioxide ($2CO + O_2 \rightarrow 2\ CO_2$). The principal source of CO poisoning is smoke inhalation from house fires, poorly functioning heating systems, and the exhaust from automobile engines (1) (*Note:* The mandate for catalytic converters in automobiles, which converts CO to CO_2, has reduced CO emissions by more than 95%.)

Pathophysiology

Carbon monoxide binds to the heme moieties in hemoglobin (at the same site that binds oxygen) to produce *carboxyhemoglobin* (COHb). The affinity of CO for binding to hemoglobin is over 200 times greater than the affinity of O_2, and CO pressures of only 0.4 mm Hg can fully saturate hemoglobin (2). The effects of COHb on systemic oxygenation are demonstrated by the oxyhemoglobin dissociation curves in Figure 53.1 (1). The curves in this graph show the relationship between oxygen tension (PO_2) and the oxygen content in blood when hemoglobin is normal (upper curve), and when COHb makes up 50% of the hemoglobin molecules (lower curve) (3). The arterial O_2 content (point A) decreases in proportion to the increase in COHb, reflecting the ability of CO to block O_2 binding to hemoglobin. The venous point (point V) on both curves was identified by assuming a normal arteriovenous O_2 content difference (CaO_2 –

CvO_2 = 5 mL/dL) for both curves. The venous PO_2 (PvO_2) is a close approximation of tissue PO_2, and it is much lower when COHb is present. This provides indirect evidence that CO poisoning impairs tissue oxygenation.

Other Effects

The affinity of CO for heme results in inhibition of other heme-containing proteins, such as myoglobin (which is responsible for O_2 storage in skeletal muscle) and cytochrome oxidase (which is responsible for the oxidative production of ATP in mitochondria) (3). Both effects promote a switch to anaerobic metabolism. CO also activates neutrophils (4), which promotes oxidative tissue injury from reactive oxygen species. (See Chapter 17, and Figure 17.1, for the production of reactive oxygen species during neutrophil activation.) These effects may play an important role in CO poisoning, because *there is a poor correlation between COHb levels and the clinical severity of CO poisoning* (4,5).

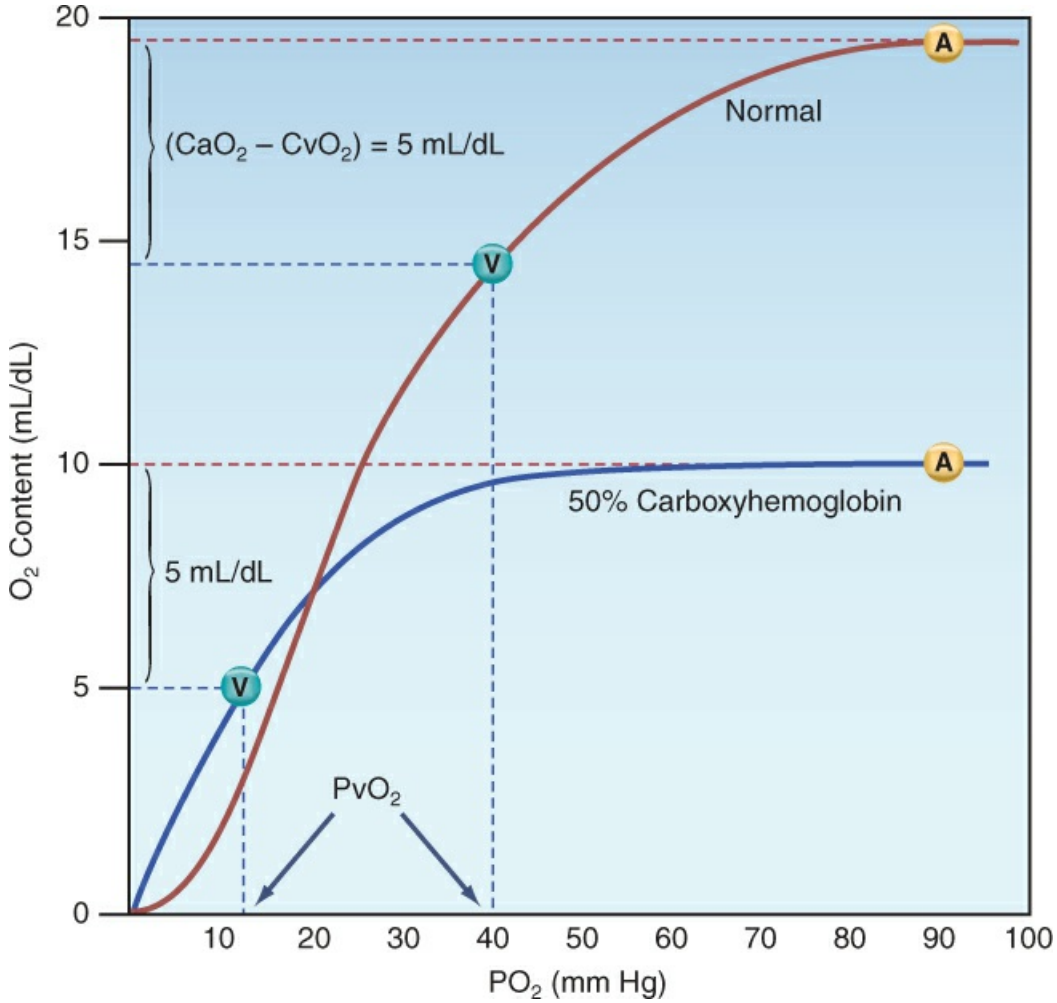

FIGURE 53.1 Influence of 50% carboxyhemoglobin on the oxyhemoglobin dissociation curve (using O_2 content instead of % hemoglobin saturation on the vertical axis). A = arterial blood, V = venous blood. The venous PO_2 (PvO_2) is a reflection of tissue PO, and is decreased by the carbon monoxide effect on hemoglobin. Curves adapted from Reference 1.

Clinical Features

The following statements summarize the clinical manifestations of CO poisoning, which are variable and nonspecific (1).

. Headache (usually frontal) and dizziness are the most common early complaints (1), and may be accompanied by drowsiness, nausea, and vomiting. As CO exposure increases, ataxia appears, along with agitation and changes in mentation (usually confusion and delirium).

. Severe cases of CO poisoning are characterized by obtundation or coma, generalized seizures, respiratory failure, often from the acute respiratory distress syndrome, hemodynamic instability, and lactic acidosis.

. A cherry-red skin color is classically described in CO poisoning (due to COHb being a brighter shade of red than oxyhemoglobin), but this is a rare occurrence (5).

Delayed Neurologic Sequelae

Symptoms of acute CO poisoning can be followed (in one to four weeks) by a neuropsychiatric syndrome that includes mental deterioration (e.g., impaired judgment, memory loss, cognitive defects), and parkinsonism (1,6). The culprit in the delayed neurologic response is unclear, because the correlation with COHb levels has been difficult to establish (1).

Diagnosis

The diagnosis of CO poisoning is not possible based on signs and symptoms alone, and requires evidence of an elevated COHb level in blood.

Carboxyhemoglobin

The measurement of hemoglobin in its different forms (oxygenated and deoxygenated hemoglobin, methemoglobin, and carboxyhemoglobin) is based on the light absorbing properties of each form. This method is known as *oximetry*, and is described in detail in Chapter 7. The following statements summarize the use of oximetry to measure COHb levels in blood.

. *Pulse oximetry is NOT reliable for the detection of COHb*. Pulse oximeters use 2 wavelengths of light to measure oxygenated and deoxygenated hemoglobin in blood. Light absorbance at one of the wavelengths (660 nm) is very similar for oxygenated hemoglobin and COHb (see Figure 7.1), so *COHb is measured as oxygenated hemoglobin (HbO_2) by pulse oximeters, which results in spuriously high readings for HbO_2* (7).

. The measurement of COHb requires an 8-wavelength oximeter (known as a CO-oximeter) that is available in most clinical laboratories. This device measures the relative abundance of all forms of hemoglobin in blood, and the abundance of each form is expressed as a percentage of the total hemoglobin in blood.

COHb levels are negligible (<1%) in healthy nonsmokers, but smokers have COHb levels of 3–5% or even higher (5). Therefore, the threshold for elevated COHb levels is 3–4% for nonsmokers, and 10% for smokers (5).

Management

The treatment for CO poisoning is inhalation of 100% oxygen. The elimination half-life of COHb is 320 minutes while breathing room air, and 74 minutes while breathing 100% oxygen (5), so *less than 1½ hours of breathing 100% oxygen should reduce COHb levels to normal*. To achieve this, high-flow, heated and humidified nasal O_2, which delivers O_2 at rates up to 40 L/min, seems the best option to ensure 100% O_2 inhalation. (High-flow nasal O_2 is described in Chapter 25, and is depicted in Figure 25.5.)

Hyperbaric Oxygen

Hyperbaric oxygen has been studied for the treatment of CO poisoning since the 1970s, and there is some evidence that it might reduce the risk of delayed neuropsychiatric sequelae (8). However, the sum of the entire experience with hyperbaric O_2 shows no convincing evidence that it is superior to "normobaric" O_2 therapy for CO poisoning (7,9).

Cardiac Concerns

Myocardial injury has been reported in close to 40% of patients with moderate to severe CO poisoning, and is a poor prognostic finding (10). Therefore, an ECG and cardiac biomarkers are recommended for all patients with moderate or severe CO poisoning (7).

Cyanide Poisoning

House fires generate hydrogen cyanide gas as well as carbon monoxide, and empiric treatment for cyanide poisoning is recommended for smoke inhalation victims who are hemodynamically unstable, or have a serum lactate level ≥10 mmol/L (5). This treatment is described in the next section.

CYANIDE POISONING

Cyanide is a lethal toxin with a nefarious history. The Nazis used hydrogen cyanide gas (Zyklon-B) for mass murder in the 1940's, and in 1978, cyanide-laced fruit drinks were used for the mass murder of more than 900 adults and children in Jonestown, Guyana (11). The principal sources of cyanide poisoning include inhalation of hydrogen cyanide gas during domestic fires (12), and oral ingestion of potassium or sodium cyanide, which is converted to hydrogen cyanide by gastric acidity (13). There is also an iatrogenic source of cyanide poisoning from vasodilator infusions with *sodium nitroprusside* (14), which should never be overlooked.

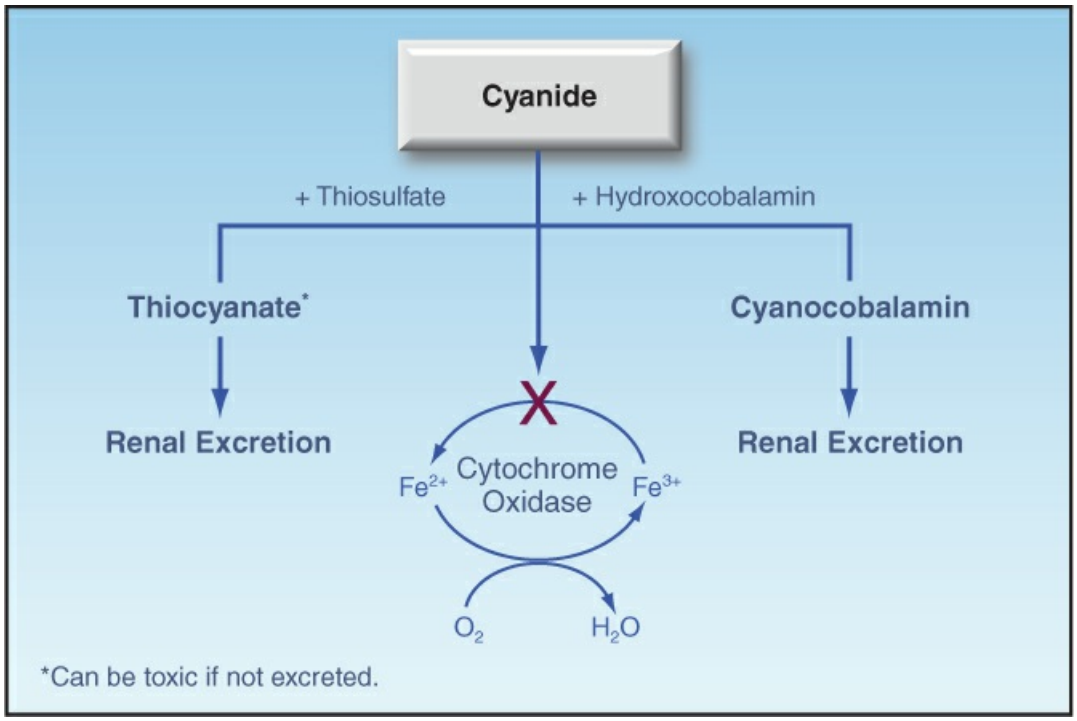

FIGURE 53.2 The actions of cyanide to inhibit cytochrome oxidase, and the clearance of cyanide by hydroxocobalamin and thiocyanate. See text for further explanation.

Pathogenesis

Cyanide ions have a high affinity for metalloproteins, including the oxidized iron (Fe^{3+}) in cytochrome oxidase and methemoglobin. Cytochrome oxidase is the last enzyme system in the electron-transport chain within mitochondria, where the electrons collected during ATP production are used to reduce oxygen to water (see Figure 53.2). Cyanide-induced inhibition of cytochrome oxidase thus halts the process of oxidative energy production in mitochondria. This impedes the uptake of pyruvate into mitochondria, and subsequently increases the production of lactic acid. The accumulation of lactate in plasma produces *a progressive metabolic (lactic) acidosis*, which *is a hallmark of cyanide poisoning*. The defect in cellular energy production is often fatal if not corrected.

Clinical Features

Early signs of cyanide poisoning include agitation, tachycardia, hypertension, and tachypnea, representing the compensatory stage of metabolic acidosis. This often progresses to loss of consciousness, bradycardia, hypotension, and cardiac arrest. Plasma lactate levels are typically very high (>10 mmol/L), and venous blood can look "arterialized" (and have a high PO_2) because of the marked decrease in tissue O_2 utilization (13). Progression is rapid after smoke inhalation, and the time from onset of symptoms to cardiac arrest can be less than 5 minutes (12). Progression can be much slower after the oral ingestion of cyanide, and clinical manifestations can take several minutes or even hours to appear (13).

Diagnosis

Cyanide poisoning is a clinical diagnosis. Whole blood cyanide levels can be used for documentation, but results are not immediately available, and cyanide antidotes must be given quickly for optimal results. The clinical diagnosis of cyanide poisoning is particularly challenging in victims of smoke inhalation, because many of the clinical features of cyanide poisoning are indistinguishable from carbon monoxide (CO) poisoning. Cyanide poisoning should be suspected if smoke inhalation is associated with hemodynamic instability, or a plasma lactate >10 mmol/L (5). However, there may not be not enough time to wait for a lactate level after smoke inhalation.

Treatment

There are three antidotes for cyanide poisoning, which are included in Table 53.1. Unfortunately, the most effective antidotes must be given intravenously, which can cause dangerous delays in treatment (especially for smoke inhalation victims).

TABLE 53.1 Antidotes for Cyanide Poisoning

Antidote	Dosing Regimens and Comments
Hydroxocobalamin	Dosing: 5 grams infused IV over 15 minutes. Give 10 grams for cardiac arrest. Comment: The antidote of choice for cyanide poisoning. May cause reddish color in urine for a few days.
Sodium Thiosulfate	Dosing: 12.5 grams in 50 mL sterile water, by IV injection. Comment: Used in combination with hydroxocobalamin. Do not use in patients with renal failure.
Amyl Nitrite Inhalant	Dosing: Inhale for 15 sec. then rest for 15 sec, and repeat if needed. Use a new ampule (0.3 mL) every 3 minutes. Comment: Used only for temporary relief when IV access not available. Contraindicated in smoke inhalation.

From References 12, 15, and 18.

Hydroxocobalamin

The antidote of choice for cyanide poisoning is *hydroxocobalamin*, a cobalt-containing precursor of vitamin B_{12} that combines with cyanide to form cyanocobalamin, which is then excreted in the urine (see Figure 53.2). The recommended dose is *5 grams, given as an IV infusion over 15 minutes* (15). A second dose of 5 grams is recommended for life-threatening cases. Hydroxocobalamin is generally considered to be safe, although it can cause a transient rise in blood pressure. It can also produce a reddish color in urine and other body fluids for a few days (16).

Sodium Thiosulfate

Sodium thiosulfate (S_2O_3) converts cyanide to thiocyanate (SCN) by the following *transulfuration reaction*:

$$S_2O_3 + CN \rightarrow SCN + SO_3 \qquad (53.1)$$

Thiocyanate is then cleared by the kidneys. Thiosulfate can be used in combination with hydroxocobalamin (17), and the recommended dose is *12.5 grams IV* (diluted in 50 mL sterile water) (18). However, thiosulfate is not recommended in patients with renal failure because *thiocyanate is a neurotoxin that can accumulate in renal failure and cause an acute psychosis* (14),

Nitrites

Nitrites enhance cyanide clearance by promoting the formation of methemoglobin ($Hb\text{-}Fe^{3+}$), which combines with cyanide to form cyanmethemoglobin: i.e.,

$$Hb\text{-}Fe^{3+} + CN \rightarrow Hb\text{-}Fe^{2+} - CN \qquad (53.2)$$

The hemoglobin-bound cyanide is eventually cleared by reacting with thiosulfate, which should be used in combination with nitrites. Unfortunately, nitrites have undesirable side effects, and *are contraindicated in smoke inhalation* (because methemoglobin promotes tissue hypoxia) (12). The only role for nitrites in cyanide poisoning is the use of inhaled amyl nitrite as a temporary measure when IV access is not available.

Cyanide Antidote Kits

There are two kits available for cyanide poisoning, but neither kit has all the antidotes.

. The Cyanokit® (14) contains 5 grams of hydroxocobalamin as a powder, but has no diluent for IV administration, and has no repeat dose of hydroxocobalamin (14). There is also no thiosulfate or amyl nitrite in this kit.

. The Cyanide Antidote Kit (18) contains 2 vials of sodium thiosulfate for injection: each vial contains 12.5 grams of sodium thiosulfate in 50 mL of sterile water. The kit also contains 12 ampules of 0.3 mL amyl nitrite for inhalation. Each inhalation should be for 15 sec, alternating with 15 sec of rest, and continued as long as needed. A new ampule should be used every 3 minutes.

It certainly would be advantageous if all the cyanide antidotes were available in a single kit.

TOXIC ALCOHOLS

Ethylene glycol and methanol are common components of household, automotive, and industrial products, and they both produce toxic syndromes that are characterized by a metabolic acidosis. They are called *toxic alcohols* (19), but this is a misnomer, because it implies that ethanol is non-toxic.

Ethylene Glycol

Ethylene glycol is the main ingredient in many automotive antifreeze and deicer products. It has a sweet, agreeable taste, which makes it a popular method of attempted suicide.

Pathogenesis

Ethylene glycol is readily absorbed from the GI tract, and 80% of the ingested dose is metabolized in the liver. The metabolism of ethylene glycol involves the formation of a series of acids, with the participation of alcohol dehydrogenase and lactate dehydrogenase enzymes, *ending with the formation of oxalic acid* (see Figure 53.3) (19). Each of the intermediate reactions involves the conversion of NAD to NADH, which promotes the conversion of pyruvate to lactate. As a result, serum lactate levels are also elevated in ethylene glycol poisoning (12). Each of the acid intermediates in ethylene glycol metabolism is a strong acid that readily dissociates, and can contribute to a metabolic acidosis. The oxalic acid also combines with calcium to form insoluble calcium oxalate crystals that precipitate in several tissues, and are particularly prominent in the renal tubules. These crystals are a source of renal tubular injury, and are visible on urine microscopy.

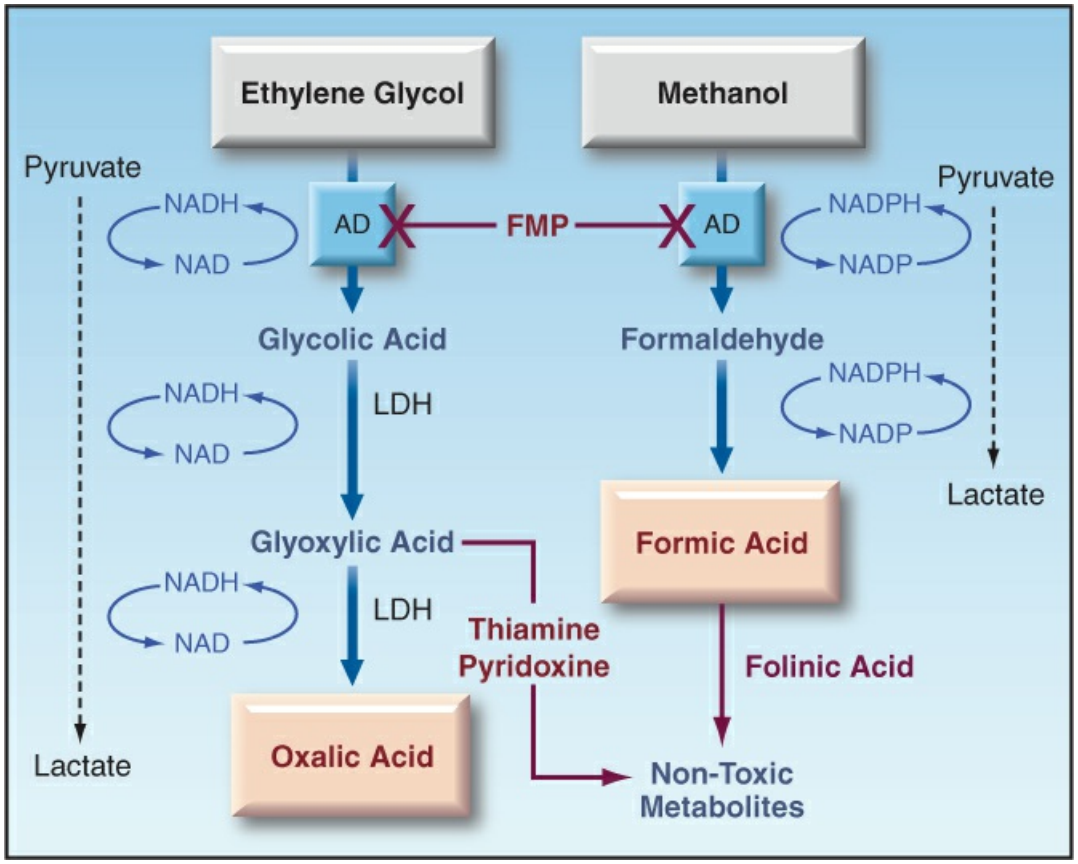

FIGURE 53.3 The metabolism of ethylene glycol and methanol in the liver. AD = alcohol dehydrogenase, LDH = lactate dehydrogenase, FMP = fomepizole.

Clinical Features

Early signs of ethylene glycol intoxication include nausea, vomiting, and apparent inebriation (altered mental status, slurred speech, and ataxia). Because ethylene glycol is odorless, there is no odor of alcohol on the breath. Severe cases are accompanied by depressed consciousness, coma, generalized seizures, renal failure, pulmonary edema, and cardiovascular collapse (19). Renal failure can be a late finding (24 hours after ingestion).

Laboratory studies show a metabolic acidosis with an elevated anion gap (due to glycolic

acid and oxalic acid) and an elevated osmolal gap (See the latter part of Chapter 31 for a description of the osmolal gap.) Serum lactate levels can be elevated, and this can be misleading, as the high anion-gap metabolic acidosis may be mistakenly attributed to the elevated lactate levels.

Plasma assays are available for ethylene glycol and glycolic acid, but neither is readily available, and decisions about acute management are based on clinical judgment. However, plasma levels of ethylene glycol and glycolic acid should be obtained for confirmatory purposes. Plasma levels of ethylene glycol that are above 20 mg/dL are considered toxic (19), but plasma glycolic acid levels are more predictive of the severity of disease, and levels above 8 mmol/L have been proposed as an indication for hemodialysis (20).

CRYSTALLURIA: Calcium oxalate crystals can be visualized in the urine in about 50% of cases of ethylene glycol poisoning (21). The presence of calcium oxalate crystals is not specific for ethylene glycol poisoning, but the shape of the crystals is more specific; i.e., thin, monohydrate crystals, like the ones shown in Figure 53.4, are more characteristic of ethylene glycol poisoning than the box-shaped dihydrate crystals (21). Most hospital laboratories do not routinely inspect urine for crystals, so make sure to request a search for crystals when a urine sample is sent to the laboratory.

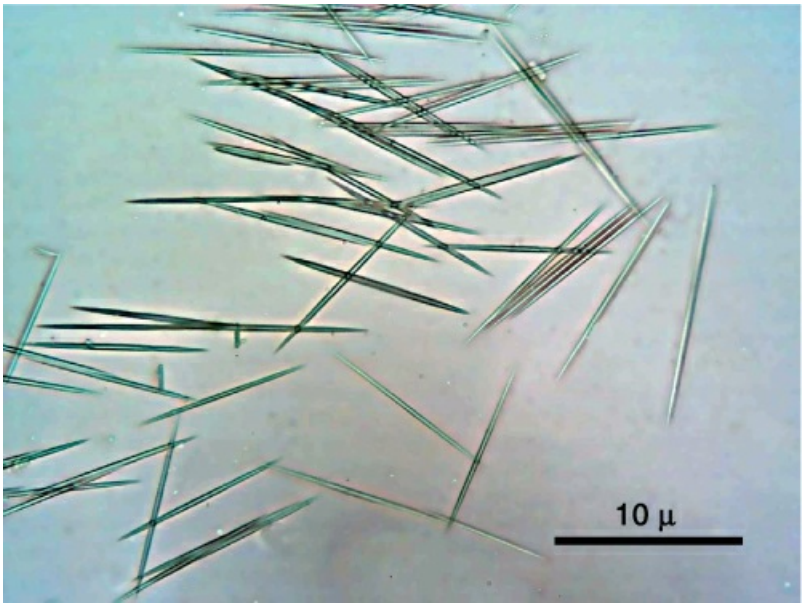

FIGURE 53.4 Microscopic appearance of calcium oxalate monohydrate crystals. The presence of these thin, needle-shaped crystals in the urine is highly suggestive of ethylene glycol poisoning.

Treatment

The management of ethylene glycol poisoning involves measures to alter the metabolism of ethylene glycol, along with hemodialysis, if necessary.

FOMEPIZOLE: Fomepizole inhibits alcohol dehydrogenase, the enzyme involved in the initial step of ethylene glycol metabolism (see Figure 53.3). The recommended dosing regimen for both

ethylene glycol and methanol poisoning is shown in Table 53.2 (19). The best results are obtained if therapy begins within 4 hours of ingestion. Fomepizole should be continued until the toxic alcohol levels in plasma have fallen to <20 mg/dL, and the metabolic acidosis has resolved.

TABLE 53.2 Dosing Regimen for Fomepizole

1. Start with an IV loading dose of 15 mg/kg.
2. Follow with a dose of 10 mg/kg IV every 12 hrs for 4 doses.
3. If the toxic alcohol level is >20 mg/dL after 4 doses, increase the dose to 15 mg/kg IV every 12 hours, and continue until the following end-points are reached:
   a. the toxic alcohol level is <20 mg/dL,
   b. the plasma pH is normal,
   c. the patient is asymptomatic.
4. If more than one hemodialysis session is required, change the dose to 15 mg/kg IV every 4 hrs, until dialysis is no longer necessary.

From Reference 19.

HEMODIALYSIS: The clearance of ethylene glycol and all its metabolites is enhanced by hemodialysis. The indications for immediate hemodialysis include severe acidemia (pH <7.1), and evidence of significant end-organ damage (e.g., coma, seizures, and renal insufficiency) (19). Multiple courses of hemodialysis may be necessary, and fomepizole dosing should be adjusted, as indicated in Table 53.2.

ADJUNCTS: Thiamine (100 mg IV daily) and pyridoxine (100 mg IV daily) are recommended to divert glyoxylic acid to the formation of non-toxic metabolites (see Figure 53.3).

Methanol

Methanol (also known as *wood alcohol* because it was first distilled from wood) is a common ingredient in shellac, varnish, paint remover or thinner, windshield washer fluid, and solid cooking fuel (e.g., Sterno® products).

Pathogenesis

Like ethylene glycol, methanol is readily absorbed from the upper GI tract, and is metabolized by alcohol dehydrogenase in the liver. The *principal metabolite is formic acid*, a strong acid that readily dissociates and produces a metabolic acidosis with a high anion gap (19). Formic acid is also a mitochondrial toxin that inhibits cytochrome oxidase and blocks oxidative energy production. Tissues that are particularly susceptible to damage are the retina, optic nerve, and basal ganglia. In one study, hypodense lesions in the basal ganglia were present on CT scan in 64% of patients with methanol poisoning (22). Methanol metabolism promotes the conversion of pyruvate to lactate in the same manner described for ethylene glycol metabolism, and lactate production is increased further by the toxic effects of formic acid.

Clinical Features

Early manifestations (within 6 hours of ingestion) include signs of apparent inebriation without

the odor of ethanol (as in ethylene glycol intoxication). Later signs (6–24 hours after ingestion) include visual disturbances (e.g., scotoma, blurred vision, complete blindness), depressed consciousness, coma, and generalized seizures (21). Examination of the retina can reveal papilledema and generalized retinal edema. The visual disturbances are characteristic of methanol poisoning, and are not a feature of ethylene glycol poisoning.

Laboratory studies show a metabolic acidosis, high anion gap, and high osmolal gap, similar to ethylene glycol poisoning. However, there is no crystalluria in methanol poisoning. A plasma assay for methanol is available, and a level above 20 mg/dL is considered toxic. However, the results of the plasma assay are not immediately available, and are not used in the decision to initiate therapy.

Treatment

Treatment for methanol poisoning is the same as described for ethylene glycol poisoning, except for the following: (a) visual impairment is an indication for dialysis in methanol poisoning and (b) folinic acid is used as adjunctive therapy in methanol poisoning, instead of thiamine and pyridoxine.

FOLINIC ACID: Folinic acid (leucovorin) can convert formic acid to non-toxic metabolites. The recommended dose is 1 mg/kg IV, up to 50 mg, at 4-hour intervals (21). Folic acid should be used if folinic acid is unavailable.

A FINAL WORD

The following points in this chapter deserve emphasis:

. Carbon monoxide poisoning can be missed if you rely on pulse oximetry readings to detect O_2 desaturation. Detection of elevated carboxyhemoglobin levels requires an 8-wavelength CO-oximeter, which is in most clinical laboratories.

. A victim of smoke inhalation who has a severe lactic acidosis or hemodynamic instability should be treated empirically for cyanide poisoning.

. Methanol and ethylene glycol poisoning should be considered in any patient who presents with a high-anion-gap metabolic acidosis of unclear etiology.

. If ethylene glycol poisoning is a consideration, inspection of the urine for calcium oxalate monohydrate crystals can provide confirmatory evidence.

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Cyanide

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Toxic Alcohols

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Section XVII

APPENDICES

When you're through learning, you're through.

Will Rogers

Appendix 1

Units and Conversions

The units of measurements in the medical sciences are taken from the metric system (centimeter, gram, second) and the Anglo-Saxon system (foot, pound, second). The metric units were introduced during the French Revolution and were revised in 1960. The revised units are called Système Internationale (SI) units and are currently the worldwide standard.

PART 1 Units of Measurement in the Système Internationale

Parameters	Dimensions	Basic SI Unit (Symbol)	Equivalencies
Length	L	Meter (m)	1 inch = 2.54 cm
Area	L^2	Square meter (m^2)	1 square centimeter (cm^2) = 104 m^2
Volume	L^3	Cubic meter (m^3)	1 liter (L) = 0.001 m^3 1 milliliter (mL) =1 cubic centimeter (cm^3)
Mass	M	Kilogram (kg)	1 pound (lb) = 453.5 g 1 kg = 2.2 lbs
Density	M/L^3	Kilogram per cubic meter (kg/m^3)	1 kg/m^3 = 0.001 kg/dm^3 Density of water = 1.0 kg/dm^3 Density of mercury = 13.6 kg/dm^3
Velocity	L/T	Meters per second (m/sec)	1 mile per hour (mph) = 0.4 m/sec
Acceleration	L/T^2	Meters per second squared (m/sec^2)	1 ft/sec^2 = 0.03 m/sec^2
Force	M x (L/T^2)	Newton (N) = kg × (m/sec^2)	1 dyne = 10^{-5} N

PART 2 Units of Measurement in the Système Internationale

Parameters	Dimensions	Basic SI Unit (Symbol)	Equivalencies
Pressure	M × (L/T^2)	Pascal (Pa) = N/m^2	1 kPa = 7.5 mm Hg = 10.2 cm H_2O 1 mm Hg = 1 × 10^{-9} torr (See conversion table for kPa and cm H_2O).

Heat	M × (L/T^2) × L	Joule (J) = N x M	1 kilocalorie (kcal) = 4,184 J
Temperature	None	Kelvin (K)	0° C = –273 K (See conversion table for °C and °F)
Viscosity	M, 1/L, 1/T	Newton × second per square meter (N • sec/m^2)	Centipoise (cP) = 10^{-3} N • sec/m^2
Amount of a substance	N	Mole (mol) = molecular weight in grams	Equivalent (Eq) = mol × valence

PART 1 Converting Units of Solute Concentration

1. For ions that exist freely in an aqueous solution, the concentration is expressed as milliequivalents per liter (mEq/L). To convert to millimoles per liter (mmol/L):

$$\frac{\text{mEq/L}}{\text{valence}} = \text{mmol/L}$$

   a. For a univalent ion like potassium (K^+), the concentration in mmol/L is the same as the concentration in mEq/L.

   b. For a divalent ion like magnesium (Mg^{++}), the concentration in mmol/L is one-half the concentration in mEq/L.

2. For ions that are partially bound or complexed to other molecules (e.g., plasma Ca^{++}), the concentration is usually expressed as milligrams per deciliter (mg/dL). To convert to mEq/L:

$$\frac{\text{mg/dL} \times 10}{\text{mol wt}} \times \text{valence} = \text{mEq/L}$$

   where mol wt is molecular weight, and the factor 10 is used to convert deciliters (100 mL) to liters.

   EXAMPLE: Ca^{++} has a molecular weight of 40 and a valence of 2, so a plasma Ca^{++} concentration of 8 mg/dL is equivalent to:

$$(8 \times 10/40) \times 2 = 4 \text{ mEq/L}$$

PART 2 Converting Units of Solute Concentration

3. The concentration of uncharged molecules (e.g., glucose) is also expressed as milligrams per deciliter (mg/dL). To convert to (mmol/L):

$$\frac{\text{mg/dL} \times 10}{\text{mol wt}} = \text{mmol/L}$$

   EXAMPLE: Glucose has a molecular weight of 180, so a plasma glucose concentration of 90 mg/dL is equivalent to: (90 × 10/180) = 5 mmol/L.

4. The concentration of solutes can also be expressed in terms of osmotic pressure, which determines the distribution of water in different fluid compartments. Osmotic activity in aqueous solutions (called osmolality) is expressed as milliosmoles per kg water (mosm/kg H_2O or mosm/kg).

   The following formulas can be used to express the osmolality of solute concentrations (n is the number of nondissociable particles per molecule).

$$\text{mmol/L} \times n = \text{mosm/kg}$$

$$\frac{\text{mEq/L}}{\text{valence}} \times n = \text{mosm/kg}$$

$$\frac{\text{mg/dL} \times 10}{\text{mol wt}} \times n = \text{mosm/kg}$$

EXAMPLE:

a. A plasma Na^+ concentration of 140 mEq/L has the following osmolality:

$$\frac{140}{1} \times 1 = 140 \text{ mosm/kg}$$

b. A plasma glucose concentration of 90 mg/dL has the following osmolality:

$$\frac{90 \times 10}{180} \times 1 = 5 \text{ mosm/kg}$$

The sodium in plasma has a much greater osmotic activity than the glucose in plasma because osmotic activity is determined by the number of particles in solution, and is independent of the size of the particles (i.e., one sodium ion has the same osmotic activity as one glucose molecule).

Apothecary and Household Conversions

Apothecary	Household
1 grain = 60 mg 1 ounce = 30 mg 1 fluid ounce = 30 mL 1 pint = 500 mL 1 quart = 947 mL	1 teaspoonful = 5 mL 1 tablespoonful = 15 mL 1 wineglassful = 60 mL 1 teacupful = 120 mL

French Sizes

French Size	Outside Diameter*	
	Inches	mm
1	0.01	0.3
4	0.05	1.3
8	0.10	2.6
10	0.13	3.3
12	0.16	4.0
14	0.18	4.6
16	0.21	5.3
18	0.23	6.0

20	0.26	6.6
22	0.28	7.3
24	0.31	8.0
26	0.34	8.6
28	0.36	9.3
30	0.39	10.0
32	0.41	10.6
34	0.44	11.3
36	0.47	12.0
38	0.50	12.6

*Diameters can vary with manufacturers. However, a useful rule of thumb is OD (mm) × 3 = French size.

Gauge Sizes

Gauge Size	Outside Diameter*	
	Inches	mm
26	0.018	0.45
25	0.020	0.50
24	0.022	0.56
23	0.024	0.61
22	0.028	0.71
21	0.032	0.81
20	0.036	0.91
19	0.040	1.02
18	0.048	1.22
16	0.040	1.62
14	0.080	2.03
12	0.104	2.64

*Diameters can vary with manufacturers.

Temperature Conversions

°C	°F	°C	°F
41	105.8	35	95

40	104	34	93.2
39	102.2	33	91.4
38	100.4	32	89.6
37	98.6	31	87.8
36	96.8	30	86
°F = (9/5 °C) + 32		°C = 5/9 (°F – 32)	

Pressure Conversions

mm Hg	kPa	mm Hg	kPa	mm Hg	kPa
41	5.45	61	8.11	81	10.77
42	5.59	62	8.25	82	10.91
43	5.72	63	8.38	83	11.04
44	5.85	64	8.51	84	11.17
45	5.99	64	8.51	85	11.31
46	6.12	66	8.78	86	11.44
47	6.25	67	8.91	87	11.57
48	6.38	68	9.04	88	11.70
49	6.52	68	9.04	89	11.84
50	6.65	70	9.31	90	11.97
51	6.78	71	9.44	91	12.10
52	6.92	72	9.58	92	12.24
53	7.05	73	9.71	93	12.37
54	7.18	74	9.84	94	12.50
55	7.32	75	9.98	95	12.64
56	7.45	76	10.11	96	12.77
57	7.58	76	10.11	97	12.90

Kilopascal (kPa) = 0.133 × mm Hg; mm Hg = 7.5 × kPa.

Appendix 2

Selected Reference Ranges

Radiation Dose in Common Radiographic Procedures

Procedure	Average Effective Dose[1]	Range
Chest x-ray (1 view) Chest x-ray (2 views) Abdomen	0.02 mSv 0.1 mSv 0.7 mSv	0.007–0.05 0.05–0.24 0.04–1.1
Head CT Chest CT Abdominal CT	2 mSv 7 mSv 8 mSv	0.9–4.0 4–18 3.5–25
Chest CT Angiography Coronary Angiography	15 mSv 16 mSv	13–40 5–32
Annual Radiation Limit[2]	50 mSv	

From Mettler FA Jr, et al. Effective doses in radiology and diagnostic nuclear medicine: A catalogue. Radiology 2008; 248:254–263.

[1] The effective dose (in millisieverts or mSv) expresses the radiation dose to all organs in the body. [2] From the Environmental Protection Agency.

Body Mass Index

Body Mass Index

WEIGHT	lbs	100	105	110	115	120	125	130	135	140	146	150	155	160	165	170	175	180	185	190	195	200	205	210	215
	kg	45.5	47.7	50.0	52.3	54.5	56.8	59.1	61.4	63.6	65.9	68.2	70.5	72.7	75.0	77.3	79.5	81.8	84.1	86.4	88.6	90.9	93.2	95.5	97.7
HEIGHT in	cm	Underweight					Healthy					Overweight					Obese				Extremely Obese				
5.'0"	152.4	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
5.'1"	154.9	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	36	37	38	39	40
5.'2"	157.4	18	19	20	21	22	22	23	24	25	26	27	28	29	30	31	32	33	33	34	35	36	37	38	39
5.'3"	160.0	17	18	19	20	21	22	23	24	24	25	26	27	28	29	30	31	32	32	33	34	35	36	37	38
5.'4"	162.5	17	18	18	19	20	21	22	23	24	24	25	26	27	28	29	30	31	31	32	33	34	35	36	37
5.'5"	165.1	16	17	18	19	20	20	21	22	23	24	25	25	26	27	28	29	30	30	31	32	33	34	35	35
5.'6"	167.6	16	17	17	18	19	20	21	21	22	23	24	25	25	26	27	28	29	29	30	31	32	33	34	34
5.'7"	170.1	15	16	17	18	18	19	20	21	22	22	23	24	25	25	26	27	28	29	29	30	31	32	33	33
5.'8	172.7	15	16	16	17	18	19	19	20	21	22	22	23	24	25	25	26	27	28	28	29	30	31	32	32
5.'9"	175.2	14	15	16	17	17	18	19	20	20	21	22	22	23	24	25	25	26	27	28	28	29	30	31	31
5.'10"	177.8	14	15	15	16	17	18	18	19	20	20	21	22	23	23	24	25	25	26	27	28	28	29	30	30
5.'11"	180.3	14	14	15	16	16	17	18	18	19	20	21	21	22	23	23	24	25	25	26	27	28	28	29	30
6.'0"	182.8	13	14	14	15	16	17	17	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27	28	29
6.'1"	185.4	13	13	14	15	15	16	17	17	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27	28
6.'2"	187.9	12	13	14	14	15	16	16	17	18	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27
6.'3"	190.5	12	13	13	14	15	15	16	16	17	18	18	19	20	20	21	21	22	23	23	24	25	25	26	26
6.'4"	193.0	12	12	13	14	14	15	15	16	17	17	18	18	19	20	20	21	22	22	23	23	24	25	25	26

Desirable Weights (in lbs.) for Adults*

Desirable Weights (in lbs.) for Adults*				
Height		Males		
Feet	Inches	Small Frame	Medium Frame	Large Frame
5	2	128–134	131–141	138–150
5	3	130–136	133–143	140–153
5	4	132–138	135–145	142–156
5	5	134–140	137–148	144–160
5	6	136–142	139–151	146–164
5	7	138–145	142–154	149–168
5	8	140–148	145–157	152–172
5	9	142–151	148–160	155–176
5	10	144–154	151–163	158–180
5	11	146–157	154–166	161–184
6	0	149–160	157–170	164–188
6	1	152–164	160–174	168–192
6	2	155–168	164–178	172–197
6	3	158–172	167–182	172–202
6	4	162–176	171–187	181–207

Height		Females		
Feet	Inches	Small Frame	Medium Frame	Large Frame
4	10	102–111	109–121	112–131
4	11	103–113	111–123	120–134
5	0	104–115	113–126	122–137
5	1	106–118	115–129	125–140
5	2	108–121	118–132	128–143
5	3	111–124	121–135	131–147
5	4	114–127	124–138	134–151
5	5	117–130	127–141	137–155
5	6	120–133	130–144	140–159
5	7	123–136	133–147	143–163
5	8	126–139	136–150	146–167
5	9	129–142	139–153	149–170
5	10	132–145	142–156	152–173
5	11	135–148	145–159	155–176
6	1	138–151	148–162	158–179

*Unclothed weights associated with the longest life expectancies. From the statistics bureau of the Metropolitan Life Insurance Company, 1983.

Peak Expiratory Flow Rates for Healthy Males

Age (yr)	Ht:	L/min			
		60″	65″	70″	75″
20		602	649	693	740
25		590	636	679	725
30		577	622	664	710
35		565	609	651	695
40		552	596	636	680
45		540	583	622	665
50		527	569	607	649
55		515	556	593	634
60		502	542	578	618
65		490	529	564	603
70		477	515	550	587

Peak Flow (L/min) = [3.95–(0.0151 × Age)] × Ht (cm).
Regression equation from Leiner GC, et al. Am Rev Respir Dis 1963; 88:646.

Peak Expiratory Flow Rates for Healthy Females

Age (yr)	Ht:	L/min 60″	65″	70″	75″
20		309	423	460	496
25		385	418	454	490
30		380	413	448	483
35		375	408	442	476
40		370	402	436	470
45		365	397	430	464
50		360	391	424	457
55		355	386	418	451
60		350	380	412	445
65		345	375	406	439
70		340	369	400	432

Peak Flow (L/min) = [2.93 –(0.0072 × Age)] × Ht (cm).

Regression equation from Leiner GC, et al. Am Rev Respir Dis 1963; 88:646.

Estimated Blood Volumes in Adults

	mL/kg Male	Female
Blood	66	60
Red Cells	26	24
Plasma	40	36

From AABB Technical Manual, 10th ed. Arlington, VA: American Association of Blood Banks, 1990.

The Confusion Assessment Method for the ICU (CAM-ICU)

The Confusion Assessment Method for the ICU (CAM-ICU)

	Yes	No
I: Acute Onset or Fluctuating Course: A. Is there evidence of an acute change in metal status? OR B. Did the abnormal behavior fluctuate during the past 24 hrs?	☐	☐
II: Inattention: Did the patient have difficulty focusing attention? (The patient can be shown 5 simple items as asked to recall the items in succession.)	☐	☐
III: Disorganized Thinking: Is there evidence of disorganized or incoherent thinking as evidenced by incorrect answers to 3 or more of the following questions? 1. Will a stone float in water? 2. Are there fish in the sea? 3. Does one pound weigh more than 2 pounds? 4. Can you use a hammer to pound a nail? AND is there difficulty following these commands? 1. Hold up this many fingers. (The examiner holds two fingers in front of the patient.) 2. Now do the same thing with the other hand (without holding the two fingers in front of the patient).	☐	☐
IV: Altered Level of Consciousness: Is the patient's level of consciousness anything other than alert, such as being hyperalert or lethargic?	☐	☐

A Yes answer to I and II, and either III or IV = Delirium.

From Ely EW, et al. JAMA 2001; 286:2703.

Appendix 3

The Body Fantastic

We cannot fathom the marvelous complexity of an organic being.

Charles Darwin

The real problem in medicine is not the cost or availability of healthcare—it is the task of fixing a machine that has about 100 trillion interconnecting parts (the estimated number of cells in the human body), none of which are visible to the naked eye. The following are some facts and factoids that highlight the complexity of the machine we are tasked to fix. This information has no direct application to the practice of medicine, and is meant only as an homage to the human body.

Our Vascular Superhighway

If all the blood vessels in the human body were placed end-to-end, they would extend about 100,000 kilometers (62,000 miles) (1), which is about 2½ times the circumference of Earth.

1. Vogel S. *Vital Circuits. On Pumps, Pipes, and the Workings of Circulatory Systems*. Oxford: Oxford University Press, 1992:16.

The Reach of Our Airways

The combined length of all the airways in the lungs is estimated at 2,500 kilometers (1,553 miles) (1), which is equivalent to the distance between London and Moscow (1,554 miles).

1. West G. *Scales. The Universal Laws of Life, Growth, and Death in Organisms, Cities, and Companies*. New York: Penguin Books, 2017:100.

The Ultimate Packing Job

The human genome is roughly 2 meters in length, yet it is packed into the cell nucleus, which is only 6 microns in diameter. This is analogous to taking a string that runs up and down the length of Manhattan (roughly 14 miles) and packing it in a tennis ball (diameter 2.6 inches).

The Complexity of the Human Genome

The DNA molecule encodes information using the pairing of four nucleotides: adenine, thymine,

cytosine, and guanine. The human genome contains about 3 billion nucleotide pairings, so the total possible sequences of nucleotide pairings is $4^{3,000,000,000}$. In comparison, the total number of electrons in the universe is estimated at 10^{80}, or 4^{133} (1).

1. Roston E. *The Carbon Age*. New York: Walker & Co, 2008:38.

The Amazing DNA Polymerase Enzyme

The human genome contains 3.2 billion nucleotide pairs, yet each replication of DNA is carried out with remarkable accuracy; i.e., a mistake occurs only once for every 10 billion nucleotides copied (1). The source of this fidelity is the DNA polymerase enzyme, which catalyzes the addition of each nucleotide to the DNA molecule, but checks to see that the nucleotide to be added is the correct one before adding it to the molecule. This means that, for every replication of the DNA molecule, the DNA polymerase enzyme "proofreads" each of the 3.2 billion nucleotide pairs to ensure accuracy of replication. This allows us to reliably transfer genetic information to our offspring.

1. DNA Replication, Repair, and Recombination. In: Alberts B, Johnson A, Lewis J, et al, eds. *Molecular Biology of the Cell*, 6th ed. New York: Garland Science, 2015:237−298.

The Celestial Reach of Our Genome

If all the DNA strands in the body were placed end-to-end, they would stretch an estimated 10 billion miles (1), which is almost three times the distance from the Sun to Pluto (3.7 billion miles).

1. Pollack R. *Signs of Life: The Language and Meanings of DNA*. London: Viking Press, 1994:19.

Human Life and an 80-watt Light Bulb

The daily energy requirement of an adult at rest is about 25 kcal/kg, which is 2,000 kcal for an 80 kg (176 lb) person. This corresponds to a hourly energy requirement of 83 kcal/hr, which is equivalent to 80 watts (1 kcal/hr=1.16 watts). Thus, the energy needed to support human life is about the same as the energy needed to power an 80-watt light bulb.

The Molecular Burden of Staying Alive

The energy used by the human body to conduct the myriad processes involved in living is derived from the production and breakdown of adenosine triphosphate (ATP). The daily production of ATP is estimated at 2×10^{26} molecules per day, which corresponds to a mass of about 80 kg (176 lb) (1). This is close to the average weight of an adult in North America (177.5 lbs) (2). This means that, each and every day, the adult human body cycles a molecular mass equivalent to its own body weight in order to stay alive.

1. West G. *Scaling*. New York: Penguin Books, 2018:100.
2. Walpole SC, Prieto-Merino D, Edwards P, et al. The weight of nations: an estimation of adult human biomass. BMC Public Health 2012; 12:439−445.

Our Erythrocyte Burden

The number of circulating red blood cells (RBCs) is normally about 5.4×10^{12}/L (5.4 trillion/L) in adult males (1). Assuming a normal blood volume of 5 liters, the total number of circulating

RBCs is 27 trillion. About 1% of circulating RBCs are replaced daily, (2) which would be 1% of 27 trillion, or 270 billion RBCs replaced daily (which is equivalent to 3.1 million RBCs/sec). Thus, to maintain the pool of circulating RBCs, the human body must manufacture 3.1 million RBCs every second.

1. Walker RH, ed. *American Association of Blood Banks Technical Manual*, 10th ed, Arlington, VA: American Association of Blood Banks, 1990.
2. Hillman RS, Finch CA. *Red Cell Manual*, 6th ed. Philadelphia: F.A. Davis Co, 1992.

The Incomprehensible Heart Beat

Every heart beat has 6 variables to consider: the part of the cardiac cycle (systole and diastole), the side of the heart (right and left side) and the ventilatory cycle (inhalation and exhalation). Considering that humans can process only 4 independent variables at one time (1), this means a single heart beat is incomprehensible at any point in time.

1. Halford GS, Baker R, McCreddon JE, Bain JD. How many variables can humans process? Psychol Sci 2005; 16:70−76.

Human Molting

The surface of the skin is composed entirely of dead cells, which are regularly shed and replaced. The average rate of shedding is estimated at 25,000 cells per minute, which means that each day, we shed about 36 million skin cells (1). Our skin regenerates about once every 30 days (2), which means that we generate a new skin about 12 times each year.

1. Bryson B. *The Body: A Guide for Occupants*. New York: Anchor Books, 2021:12.
2. Epidermis and its Renewal by Stem Cells. In: Alberts B, Johnson A, Lewis J, et al, eds. *Molecular Biology of the Cell*, 4th ed. New York: Garland Science, 2002.

Counting the Connections in the Cerebral Cortex

The number of synaptic connections in the cerebral cortex is estimated at one million billion, or 10^{15} (1). If you were to count to this number at a rate of one number per second (one mississippi, two mississippi, etc.), it would take about 32 million years to complete the task.

1. Edelman G. *Bright and Brilliant Fire. On the Matters of the Mind*. New York: Basic Books, 1992.

The Storage Capacity of the Brain

The popular claim that we use only a small fraction of our brain's capacity is supported by the report of a Japanese mnemonist (an individual who is skilled at retrieving information from memory) named Akira Hiraguchi, who memorized the sequence of numbers in Pi to 83,431 digits. It took him 16 hours and 28 minutes to recite all the numbers (1).

1. Foer J. *Moonwalking with Einstein. The Art and Science of Remembering Everything.* London: Penguin Books, 2011.

Recommendation

If you enjoy the kind of numerical approach to the human body used in this Appendix, you might also enjoy the following text: Milo R, Phillips R. *Cell Biology by the Numbers*. New York: Garland Science, Taylor & Francis Group, 2016.

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Page numbers followed by *f* indicate figures and those followed by *t* indicate tables.