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Dedication

This fifth edition of *Critical Care Medicine—The Essentials* is dedicated to my admired friend and coauthor of the initial four, Arthur P. Wheeler. Over the years, he was first my resident and fellow, then my collaborator and colleague. To those who knew him well, Art was an inspiring example of what is best in academic medical practice—a brilliant, incisively logical, well informed, straight shooting, innovative physician whose intellectual honesty and capability was matched by his empathy for his students, coworkers, and patients. With these qualities, Art contributed immensely to the Vanderbilt medical community and rose quickly to national prominence in our field of intensive care. Because he was practically minded, we could always count on him to drill to the core of the problem and then work to resolve it. Among many notable accomplishments, he shared leadership of the ARDS Network studies that helped set durable standards of care regarding safe ventilator settings, fluid management, and vascular catheter use. As an educator, Art had few peers and garnered numerous teaching awards, locally and at the national level. In his later years, he poured his energy and talents into the development of an outstanding advanced practice nursing program at Vanderbilt, years before the concept had taken hold in our field and gained its current enthusiastic attention. As was often the case, he saw the logic and need for such action well before the rest of us. As director of the Vanderbilt Medical ICU for more than two decades, he was recognized across disciplines by trainees, physicians, and nurses alike as a master intensivist gifted with rare bedside abilities. Devoted to his family and a man for all seasons, Art loved varied forms of music and became an instrumentrated airplane pilot as well as a hobby farmer. With high-level accomplishments coupled to his adventurous spirit, engaging personality, ready humor, wisdom, and dedication to what’s best in medicine, Art left a lingering example in science, education, and patient care for all to remember and emulate.

John J. Marini
Preface

Critical care is a high-stakes activity—from both outcome and cost perspectives. What should a young intensivist be taught and a seasoned practitioner ideally know? Our worlds of medical education and practice continue to change quickly. While electronic retrieval of patient records and information from scientific literature is of immeasurable help, electronically facilitated submission, peer review, and production methods have accelerated publication turnover. Pressures to shorten time in hospital and improve documentation tug the team toward the computer desk and away from the patient, placing strains on face-to-face communications among doctor, patient, family, and nurse. Because of mandated and pragmatic changes in practice, there has been a dramatic shift in care from a “one doctor-one patient” relationship to one in which there are frequent personnel changes. The chances for error or miscommunication in this evolving system are magnified. Simultaneously, older patients with chronic multisystem dysfunction and attendant complex problems account for a growing fraction of those admitted. While practicing on the cutting edge of intensive care medicine has always been challenging, there now seems more to know and too much to keep track of. At times, we do not seem to be keeping up.

Another worrisome trend seems clear. In this exciting age of molecular medicine, mastery of bedside examination and physiology has been deemphasized. Simultaneously, clinical research has shifted from exploration of everyday problems confronted at the bedside to large population-based interventional trials. When well done (and we are steadily getting better at them), these studies hold considerable value and often help decide initial “best practice” for many patients. Yet, clinical trials will never inform all decisions, and it is incumbent upon the practitioner to know when published clinical research does not apply to the patient at hand and to recognize when the course suggested by trial results should be ignored or highly modified. Physicians who apply “best practice” to the individual cannot rely only on protocols and the latest guidelines.

Recommendations come into and drop out of favor, but physiologic principles and fundamentals of critical care change very little. Because real-world problems are complex and treatment decisions interwoven, well-honed analytical skills are indispensable. To personalize critical care requires gathering and integration of a broad information stream, interpreted against a nuanced physiological background. Management must be guided by informed judgment, applying the best information presently known, and influenced by core physiological principles. Once made, the intervention must often be revised, guided by thoughtful observation of the patient's idiosyncratic response. Multidisciplinary cooperation among caregivers is essential to the success of these efforts.

Cardiorespiratory physiology forms the logical base for interpreting vital observations and delivering effective critical care. Committed to short-loop feedback and “midcourse” corrections, the intensivist should be aware of population-based studies of similar problems but not enslaved to their results. Likewise, it is important to realize that treatments that improve physiological end points do not always translate into improved patient outcomes and that failure of a patient to respond as expected to a given treatment does not invalidate that intervention for future patients. Add to these considerations the traits of cost consciousness, empathy, and effective communication, and you are well positioned to deliver cost-effective, quality care in our demanding practice environment.

Multiauthored books—even the best of them—have chapters of varying style and quality that are often lightly edited. We believe that a book intended for comprehension is best written with a single voice and consistent purpose. Therefore, every chapter in this book was written and revised by the two authors. After many years of working together in clinical practice, research, and education, we have felt free to comment freely, quibble, complain, and edit each other's work. Sadly, the coauthor of the first four editions, Art Wheeler—a brilliant physician, leader, and close friend, passed on prematurely 3 years ago. Fortunately, his place has been taken for this fifth edition by another, David Dries, whose expertise in surgery and trauma has added immeasurably to
specialties, we practice in different dedicated ICUs of the same referral and community general hospital (Regions Hospital, St. Paul, MN). Yet, as investigators and professors of Medicine and Surgery of the University of Minnesota, our research and educational interests are well aligned. Close collaboration between medical and surgical professors in an educational effort of this type is quite unusual and may be unique. Whatever the truth of that, this diversity adds breadth and helps keep perspective on what is “essential”—or at least what's valuable and interesting to know in today's practice.

Since our last edition, major insights and changes in practice have enriched our evolving field. Among the most prominent of these are neurological critical care, bedside ultrasonography, and interventional radiology. There has been dawning awareness and prioritization of the need to be less invasive and to prevent the postintensive care syndrome. Although these now receive special emphasis, virtually every chapter has been thoroughly revised and updated. Trauma and surgical critical care material, as well as illustration content, have been markedly expanded and refined.

As before, we have tried to extract what seem to be those grounding bits of knowledge that have shaped and reshaped our own approaches to daily practice. We titled this book “The Essentials” when it was first written, but admit that in places it now goes into considerable depth and quite a bit beyond basic knowledge; hence, the slightly modified title. Our own tips and tricks—useful pearls that we think give insight to practice—have been sprinkled liberally throughout. This book was written to be read primarily for durable understanding; it is not intended for quick lookup on-the-fly. It is not a book of quick facts, bullet points, checklists, options, or directions. It would be difficult to find a white coat pocket big enough to carry it along on rounds. Depth of treatment has not been surrendered in our attempt to be clear and concise.

The field of critical care and the authors, both once young and inexperienced, have now matured. Fortunately, we remain committed to caring for the sickest patients, discovering new ways to understand and more effectively confront disease, and passing on what we know to the next generation. Many principles guiding surgery and medicine are now time-tested and more or less interchangeable. For the fifth edition, we have carefully examined and updated the content of each chapter, added and modified many illustrations, expanded content, and in a few cases, discarded what no longer fits. Mostly, however, we fine-tuned and built upon a solid core. This really is no surprise—physiologically based principles endure. It is gratifying that most of what was written four editions ago still seems accurate—and never more relevant.

John J. Marini
David J. Dries
Acknowledgments

Of all the paragraphs in this book, this one is among the most difficult to write. Perhaps it is because so many have helped me reach this point—some by their inspiring mentorship, some by spirited collaboration, some by invaluable support, and some by enduring friendship. I hope that those closest to me already know the depth of my gratitude. A special few have given me far more than I have yet given back. The debts I owe to Len Hudson, Bruce Culver, Luciano Gattinoni, and Elcee Conner cannot easily be repaid. By their clear examples, they have shown me how to combine love for applied physiology, scientific discovery, and education—never forgetting that the first priorities of medicine are to express compassion for and connection with others while advancing patient welfare.

“Each wave owes the essence of its line only to the withdrawal of the preceding one.” (Andre Gide)

John J. Marini

As word of my involvement in this book spread around our hospital, many colleagues offered advice and support ranging from images and algorithms to reality checks and encouragement. I would like to acknowledge the following individuals in this regard: Kim Cartie-Wandmacher, PharmD; Hollie Lawrence, PharmD; Jeffrey Evens, TSC; Jody Rood, RN; Carol Droegemueller, RN; Christine Johns, MD; Azhar Ali, MD; Don Wiese, MD; Andy Baadh, MD; Richard Aizpuru, MD; and Haitham Hussein, MD.

To Barbara and my family, please accept my thanks for prayers, guidance, and support. Our children and grandchildren have blessed and inspired us.

Finally, thanks to my colleagues on the faculty and staff at Regions Hospital for all they have taught me.

David J. Dries
Special Thanks

The authors gratefully acknowledge collaboration of the following contributors on this Fifth Edition:

Dr. Andrew Hartigan for help in the revision of Chapter 11; Kim Cartie-Wandmacher, PharmD, for the revision of Chapter 15; and Julie Jasken, RD, for the revision of Chapter 16. The expert, uplifting and tireless contributions of Sherry Willett at Regions Hospital, as well as those of the well-tuned production team of Keith Donnellan, Timothy Rinehart, and Jennifer Clements are sincerely appreciated.

John J. Marini
David J. Dries
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• Key Points

1. Because of differences in wall thickness and ejection impedance, the two sides of the heart differ in structure and sensitivity to preload and afterload. The normal right ventricle is more sensitive to changes in its loading conditions than the left. When failing or decompensated, both ventricles are preload insensitive and afterload sensitive.

2. Right ventricular afterload is influenced by hypoxemia and acidosis, especially when the capillary bed is diminished and the vascular smooth musculature is hypertrophied, as in chronic lung disease. The ejection impedance of the left ventricle is conditioned primarily by peripheral vascular tone, wall thickness, and ventricular volume, except when there is an outflow tract narrowing or aortic valve dysfunction.

3. Regulating cardiac output to metabolic need requires appropriate values for average heart rate and stroke volume. Either or both may be the root cause of failing to do so.

4. Even when systolic function is well preserved, impaired ventricular distensibility and failure of the diseased ventricle to relax in diastole often produce pulmonary vascular congestion and predispose to “flash pulmonary edema.” Echocardiographic diastolic dysfunction often precedes heart failure and commonly develops against the background of systemic hypertension, ischemia, or other diseases that reduce left ventricular compliance.

5. The relationship of cardiac output to filling pressure can be equally well described by the traditional Frank-Starling relationship or by the venous return curve. The driving pressure for venous return is the difference between mean systemic pressure (the average vascular pressure in the systemic circuit) and right atrial pressure. Venous resistance is conditioned by vascular tone and by anatomic factors influenced by lung expansion. At a given cardiac output, mean systemic pressure is determined by venous tone and degree of vascular filling.

6. Radiographic evidence of acute heart failure includes perivascular cuffing, a widening of the vascular pedicle, blurring of the hilar vasculature, and diffuse infiltrates that tend to spare the costophrenic angles. Lung ultrasound reveals characteristic signs. Radiographic infiltrates tend to lack air bronchograms and are seldom accompanied by an acute change in heart size. Chronic congestive heart failure is typified by Kerley B lines, dilated cardiac chambers, and increased cardiac dimensions.

7. The key directives in managing cor pulmonale are to maintain adequate right ventricle filling, to reverse hypoxemia and acidosis, to establish a coordinated cardiac rhythm, to reduce oxygen demand, to avoid both overdistention and derecruitment of lung tissue, and to treat the underlying illness.

8. Pericardial tamponade presents clinically with venous congestion, hypotension, narrow pulse pressure, distant heart sounds, and equalized pressures in the left and right atria. Diastolic pressures in both ventricles are similar to those of the atria.

CHARACTERISTICS OF NORMAL AND ABNORMAL CIRCULATION

Anatomy
Cardiac Anatomy

The circulatory and respiratory systems are tightly interdependent in their primary function of delivering appropriate quantities of oxygenated blood to metabolizing tissues. The physician’s ability to deal with hemodynamic dysfunction requires a well-developed understanding of the anatomy and control of the circulation under normal and abnormal conditions. The bloodstream’s interface with the airspace (the alveoli) together with cardiac check valves divide the circulatory path into two functionally distinct limbs—right, or pulmonary, and left, or systemic. Except during congestive failure, the atria serve primarily as reservoirs for blood collection, rather than as key pumping elements. The right ventricle (RV) is structured differently than its left-sided counterpart (Table 1-1). Because of the low resistance of the pulmonary vascular bed, the normal RV generates mean pressures only one seventh as great as those of the left side while driving the same output. Consequently, the free wall of the RV is normally thin, preload sensitive, and poorly adapted to an acute increase of afterload. The thicker left ventricle (LV) must generate sufficient pressure to drive flow through a much greater and widely fluctuating vascular resistance. Because the RV and LV share the interventricular septum, circumferential muscle fibers, and the pericardial space, their interdependence has important functional consequences. For example, when the RV swells in response to increased afterload, the LV becomes functionally less distensible, and left atrial pressure tends to increase. At the same time, the shared muscle fibers allow the LV to assist in generating the required rise in RV and pulmonary arterial pressures. Ventricular interdependence is enhanced by processes that crowd their shared pericardial fossa: high lung volumes, high heart volumes, and pericardial effusion.

<table>
<thead>
<tr>
<th>Table 1-1. Right Versus Left Heart Properties</th>
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<tbody>
<tr>
<td><strong>Right Heart</strong></td>
</tr>
<tr>
<td><strong>Normal</strong></td>
</tr>
<tr>
<td>Preload sensitivity</td>
</tr>
<tr>
<td>Afterload sensitivity</td>
</tr>
<tr>
<td>Contractility</td>
</tr>
<tr>
<td>Effects of: Afterload (General)</td>
</tr>
<tr>
<td>Pleural pressure</td>
</tr>
<tr>
<td>pH</td>
</tr>
<tr>
<td>Hypoxemia</td>
</tr>
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<td>Response to inotropic and vasoactive drugs</td>
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</table>

*aNot including aortic valve disease.*
Coronary Circulation

The heart is nourished by the coronary arteries, and its venous outflow drains into the coronary sinus that opens into the right atrium. The right coronary artery emerges anteriorly from the aorta, distributing to the RV, to the sinus and atrioventricular (AV) nodes, and to the posterior and inferior surfaces of the LV. The left coronary system (circumflex and left anterior descending arteries) nourishes the interventricular septum, the conduction system below the AV node, and the anterior and lateral walls of the LV. If the heart were to relax completely, the difference between mean arterial pressure (MAP) and coronary sinus pressure would drive flow through the coronary circulation. However, because aortic pressure varies continuously and because the tension within the myocardium that surrounds the coronary vessels influences the effective downstream pressure, perfusion varies with the phases of the cardiac cycle. The LV is perfused most actively in early diastole—not when aortic pressure is at its maximum but when myocardial tension is least. The LV myocardial pressure is highest close to the endocardium and lowest near the epicardium. Hence, under stress, the endocardium is more likely to experience ischemia.

Coronary blood flow normally parallels the metabolic activity of the myocardium. Because changes in heart rate are accomplished chiefly by shortening or lengthening diastole, tachycardia reduces the cumulative time available for diastolic perfusion while increasing the heart's need for oxygen. This potential reduction in mean coronary flow is normally overridden by vasodilatation. However, coronary disease prevents full expression of such compensation. During bradycardia, longer periods of time are available for diastolic perfusion and metabolic needs are less. However, diastolic myocardial fiber tension rises as the heart expands, and marked bradycardia may simultaneously lower both mean arterial and coronary perfusion pressures.

Vascular Anatomy

Left Side

Between heartbeats, the continuous flow of blood from the heart to the periphery is maintained by the recoil of elastic vessels that were distended during systole. Arterioles serve as the primary resistive elements, and by adjusting their caliber, these small vessels regulate tissue blood flow and aid in the control of arterial pressure. The true capacitance vessels forming the reservoir of the circulation are the venules and small veins. At any one time, only a minority of the total capacitance bed is recruited or distended and only a portion of the total blood volume actively circulates. The precise distribution of the circulating blood volume among various tissue beds is governed by metabolic or functional requirements and gated by arteriolar vasoconstriction. When under physiologic stress, the capacitance bed contracts or expands in support of the circulating volume (Fig. 1-1).
FIGURE 1-1. The underfilled or contracted peripheral vasculature (left) may not improve tissue perfusion and/or reverse shock physiology in response to vasopressor agents. The adequately filled and stressed vascular network (right) is better primed to increased blood pressure and perfusion of pressure dependent tissue beds when a vasopressor/inotrope is added.

**Right Side**

In the low-pressure pulmonary circuit, relatively few structural differences distinguish normal arteries from veins. The pulmonary capillary meshwork, however, is even more luxuriant and well filled than in the periphery. Apart from innate anatomy, blood flow distribution is influenced by gravity, alveolar pressure, regional pleural pressures, oxygen tension, pH, circulating mediators, and chemical stimuli (e.g., nitric oxide).

**Circulatory Control**

**Determinants of Cardiac Output**

When averaged over time, cardiac output (product of heart rate and stroke volume) must match the metabolic requirements. In a real sense, metabolic activity regulates the cardiac output of a healthy individual; insufficient cardiac output activates inefficient anaerobic metabolism that cannot be sustained indefinitely. Agitation, anxiety, pain, shivering, fever, and increased breathing workload intensify systemic O₂ demands. In the critical care setting, matching output to demand is often achieved with the help of sedative, analgesic, antipyretic, inotropic, or vasoactive agents. It is important to remember that increasing or decreasing cardiac output can reflect shifting O₂ demands, rather than a change in ventricular loading conditions or response to therapeutic intervention.
Imaired hearts are abnormally sensitive to afterload but show blunted responses to preload augmentation.

Although the precise mechanism that links output to metabolism remains uncertain, the primary determinants of stroke volume are well defined: precontractile fiber stretch in diastole (preload), the tension developed by the muscle fibers during systolic contraction (afterload), and the forcefulness of muscular contraction under constant loading conditions (contractility) (Fig. 1-2). Factors governing these determinants, as well as their normal values, differ for the two ventricles, even though over time the average stroke volume of both ventricles must be equivalent.

**Determinants of Stroke Volume—General Concepts**

**Preload**

According to the Frank-Starling principle, muscle fiber stretch at end diastole influences the extent of cardiac ejection. The tendency of ejected volume to increase as the transmural filling pressure rises normally constitutes an important adaptive mechanism that enables moment-by-moment adjustments to changing venous return. During heart failure, the Starling curve flattens, and the ventricle becomes preload insensitive—higher filling pressures become necessary to achieve a similar output. Although preload parallels end-diastolic ventricular volume, myocardial remodeling can gradually modify the relationship between absolute chamber volume and preload. Therefore, muscle fiber stretch within a chronically dilated heart may not differ significantly from normal. End-diastolic volume is determined by ventricular compliance and by the pressure distending the ventricle (the transmural pressure). Transmural pressure is the difference between the intracavitary and juxtacardiac pressures. In comparison to the LV, the normal RV operates with a comparatively steep relationship between transmural pressure and ventricular volume. A poorly compliant ventricle, or one surrounded by increased intrathoracic or pericardial pressure, requires a higher intracavitary pressure to achieve any specified end-diastolic volume and degree of precontractile fiber stretch (Fig. 1-3). The cost of higher filling pressure may be impaired myocardial perfusion or pulmonary edema. Functional ventricular stiffening can result from myocardial disease, pericardial tethering, or extrinsic compression of the heart (Table 1-2). The precise position of the ventricle on the Starling curve is difficult to determine. However, studies of animals and normal human subjects suggest that there is little preload reserve in the supine position and that, once supine, further increases in cardiac output are met primarily by increases in heart rate and/or ejection fraction. Thus, the Frank-Starling mechanism may be of most importance during hypovolemia and in the upright position.
FIGURE 1-3. Concept of transmural pressure. The muscle fiber tensions that determine preload and afterload are developed by pressure differences across the ventricle. For example, in diastole, a measured intracavitary pressure of 15 mm Hg may correspond to a large or small chamber volume and myocardial fiber tension, depending on the compliance of the ventricle and its surrounding pressure.

Table 1-2. Reduced Diastolic Compliance

<table>
<thead>
<tr>
<th>Myocardial Thickening or Dysfunction</th>
<th>Pericardial Disease</th>
<th>Extrinsic Compression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia/infarction</td>
<td>Tamponade</td>
<td>PEEP/hyperinflation</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Constriction</td>
<td>Tension pneumothorax</td>
</tr>
<tr>
<td>Infiltration</td>
<td></td>
<td>RV dilation</td>
</tr>
<tr>
<td>Congenital defect</td>
<td></td>
<td>LV crowding</td>
</tr>
<tr>
<td>Valvular dysfunction</td>
<td></td>
<td>Impaired chest wall compliance</td>
</tr>
</tbody>
</table>

**Diastolic Dysfunction**

Diastole is usually considered a passive period in which transmural pressure distends elastic heart muscle. In normal individuals and many patients with heart disease, this approximation is more or less accurate. However, diastole is more properly considered an energy-dependent active process. (In fact, in some instances, more myocardial oxygen may be consumed in diastole than in systole.) Failure of the heart muscle to relax at a normal rate (secondary to ischemia, long-standing hypertension, or hypertrophic myopathy) can cause sufficient functional stiffening to produce pulmonary edema despite preserved systolic function. As defined by echocardiography, many apparently normally functioning elderly adults have abnormal patterns of cardiac relaxation. Perhaps one third or more of adult patients with congestive heart failure (CHF) develop symptoms on this basis, with the incidence increasing markedly with advancing age. Key echocardiographic features of diastolic dysfunction are described in Chapter 2. Diastolic dysfunction often precedes systolic dysfunction and should be considered an early warning sign of deterioration. Although diastolic and systolic impairments often coexist, the diastolic dysfunction syndrome is an especially likely explanation when signs of pulmonary
congestion predominate over those of systemic perfusion in the absence of mitral valve dysfunction. In all patients with diastolic dysfunction, the early rapid filling phase of ventricular diastole is slowed, and the extent of ventricular filling becomes more heavily influenced by terminal-phase atrial contraction. Sudden loss of the atrial “kick” often precipitates congestive symptoms. Flash pulmonary edema is often the consequence of sudden diastolic dysfunction resulting from ischemia, tachycardia, or atrial fibrillation. Diastolic dysfunction should be suspected when congestive symptoms develop despite normal systolic function in predisposed patients. Confirmation requires ancillary testing by echocardiography, radionuclide angiography, contrast ventriculography, or other imaging method. With all techniques, attention must be focused on diastole, particularly during the phase of rapid filling. In most institutions, echocardiography has become the method of choice for critically ill patients because of its convenience and reliability. Indicators of mitral valve function such as deceleration time, early diastolic (E) to late diastolic (A) wave velocity ratio, and isovolume relaxation time are helpful. Signals of the required clarity are often impossible to obtain, however, in the critically ill patient, particularly with transthoracic (as opposed to transesophageal) imaging. Regarding treatment, control of blood pressure, heart rate, and ischemia are the essential objectives. Diuretics are indicated to relieve congestive symptoms. Calcium channel blockers (e.g., verapamil, diltiazem, nifedipine) have been demonstrated to be useful in animal studies and in humans with hypertrophic cardiomyopathy. Selective β-blockers (e.g., metoprolol, carvedilol) can help reduce tachycardia, lower blood pressure, and promote long-term remodeling but must be chosen wisely and used with extreme caution when significant systolic dysfunction, conduction system disturbance, or bronchospasm coexist. Predictably, inotropes do not improve diastolic function.

Afterload
Although afterload is often equated with elevations of blood pressure or vascular resistance, it is better defined as the muscular tension that must be developed during systole per unit of blood flow. As such, the systolic wall stress is affected by blood pressure, wall thickness, and ventricular volume. In the normal heart, moderate changes in afterload are usually countered by increases in contractility, preload, or heart rate, so that forward output is usually little affected. Heart size remains small, and filling pressures do not rise excessively. However, once preload reserves have been exhausted, raising afterload can profoundly depress cardiac output if contractile force and/or heart rate do not compensate. Just as the relationship between preload and stroke volume rises more steeply for the right than for the LV, so too is the normal RV more sensitive than the left to changes in afterload (Fig. 1-2). The dilated chambers of a failing heart—both right and left—are inherently afterload sensitive (Fig. 1-2). Cardiomegaly and mitral regurgitation are clinical findings that help identify potential candidates for afterload reduction. Quantitative assessment of ejection impedance can be made by determining pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR). These indices, the quotients of driving pressure and cardiac output across their respective beds, are calculated as if the blood flow fulfilled the assumptions of Poiseuille law. Because cardiac output must be interpreted relative to body size, both indices have a wide range of normal values. Although SVR rising in response to adrenergic tone or drug treatment helps support the upstream arterial pressure that perfuses certain critical tissue beds (e.g., kidney) when cardiac output falls, elevating the vascular resistance may impair downstream capillary filling in others. Moreover, in aggregate, vascular impedance may rise sufficiently to compromise cardiac output. Judicious reduction of arterial vessel tone may then allow cardiac output to improve and vital organ perfusion to increase, while maintaining an acceptable blood pressure.

Chamber diameter also impacts afterload. In a dilated chamber, higher systolic fiber tension must be generated to produce a given intracavitary pressure, especially in fibers on the periphery. Thus, a diuretic or selective venodilator (nitroglycerine) may reduce afterload as well as preload. Apart from vessel length and diameter, blood viscosity is an important determinant of rheology and effective afterload. Blood viscosity rises nonlinearly
with hematocrit. With increasing hematocrit, crowded erythrocytes pass more sluggishly through tissues, and effective \(O_2\) transport eventually reaches a maximum, the value of which depends on circulating blood volume relative to vascular capacity (Fig. 1-4). Individual tissue beds appear to have different tolerances to changes in hematocrit and different optimal values for oxygen extraction. Viscosity may also rise dramatically in the settings of hypothermia or hyperproteinemia.

FIGURE 1-4. Increasing hematocrit helps open tissue beds and deliver \(O_2\), when open. However, at very high values seldom encountered in the ICU, hematocrit increases viscosity, impairs perfusion, and reduces \(O_2\) delivery.

**Pleural Pressure and Afterload**

Systolic pressure is a marker of the highest intracavitary pressure developed by contracting muscle fibers. The intracavitary pressure is a result of muscular forces and the regional pleural pressure that surrounds the heart. Variations in pleural pressure may significantly alter afterload and therefore, the function of the compromised LV. The paradoxical pulse observed during acute asthma results in part from inspiratory afterloading of the LV. When the pressure that surrounds the heart declines, greater muscle fiber tension must be developed during systole to generate intracavitary and systemic blood pressures. Such alterations of ventricular loading conditions help explain why vigorous breathing efforts impair the function of the ischemic or failing heart.

Right ventricular afterload tends to rise nonlinearly with increasing lung volume. The pulmonary vascular pressure-flow relationship may differ slightly for positive versus negative pressure breathing. However, the RV afterload corresponding to any given lung volume is not greatly influenced by changes of pleural pressure, because the vessel that accepts its outflow (the pulmonary artery) is subjected to similar variations in pressure.

**Contractility**
Many stimuli compete to influence the contractile state of the myocardium. Sympathetic impulses, circulating catecholamines, acid-base and electrolyte disturbances, ischemia, anoxia, and chemodepressants (e.g., drugs, mediators, toxins) or hormones (e.g., high dose insulin) may influence ventricular performance, independent of changes in preload or afterload (Fig. 1-5). Contractility is sometimes impaired transiently after blunt cardiac trauma, during intense adrenergic receptor stimulation (stress cardiomyopathy), or when ischemic myocardium is reperfused (e.g., after cardiopulmonary resuscitation, angioplasty, or lysis of coronary thrombosis). Such “stunned myocardium” may stage a complete recovery after several days of transient dysfunction. No physical sign reliably reflects altered contractility. An $S_3$ gallop, narrow pulse pressure, and poorly audible heart tones suggest impaired contractility, but these signs are difficult to quantify and are influenced by myocardial compliance, intravascular volume status, and vascular tone. Radionuclide ventriculograms and echocardiography provide excellent noninvasive means of determining ventricular size and basal contractile properties of the LV but are not well suited to continuous monitoring. The commonly used “ejection fraction” is influenced by the loading conditions of the heart. Two-dimensional echocardiographic images may misrepresent three-dimensional changes in chamber geometry.

**FIGURE 1-5. Transmural ventricular pressure volume loops. Left:** Four complete cardiac cycles are represented for different states of ventricular filling. The end-diastolic pressure volume relationship defines the Frank-Starling curve. During each cycle, there are sequential stages of diastolic filling, isovolumic contraction, active systolic ejection, and isovolumic relaxation. The end-systolic pressure volume relationship (ESPVR) correlates well with contractility. **Right:** As the myocardium is stimulated by catecholamines, the slope of the ESPVR increases, resulting in a greater pressure and ejection fraction during systole for any degree of diastolic filling.

**Heart Rate**

Changes in the rate of the healthy heart result from the interplay between the two divisions of the autonomic nervous system. Ordinarily, parasympathetic tone predominates. (When both divisions of the autonomic nervous system are blocked, the intrinsic heart rate of young adults rises from approx. 70 to 105 beats/min.) The heart's ability to respond to an increased demand for output is largely determined by its capacity to raise the heart rate appropriately. Pathological bradycardias often depress cardiac output and $O_2$ delivery, especially when a diseased or failing ventricle is unable to call upon a preload reserve. Relative bradycardia is often observed in the clinical setting—a “normal” heart rate is not logically appropriate for a stressed patient with high $O_2$ demands or impaired myocardium. Because two key determinants of oxygen delivery are affected, bradycardia induced by
profound hypoxemia depresses O₂ delivery and may rapidly precipitate circulatory collapse. Marked increases in heart rate may also lead to circulatory depression when they cause myocardial ischemia, or when reduced diastolic filling time or loss of atrial contraction impair ventricular preload. (Good examples include mitral stenosis and diastolic dysfunction.) As a general rule, sinus heart rates exceeding (220 - age)/min reduce cardiac output and myocardial perfusion, even in the absence of ischemic disease or loss of atrial contraction.

(To illustrate, sinus-driven heart rate should not exceed 150 beats/min in a 70-year-old patient.)

**Peripheral Circulation**

Vascular tone is integral to cardiac output regulation—the heart cannot pump what it fails to receive in venous return, and vasoconstriction is a key determinant of afterload. In fact, control of cardiac output may be viewed strictly from a vascular perspective (Fig. 1-6). Under steady-state conditions, venous return is proportional to the quotient of venous driving pressure and resistance. Under most circumstances, the downstream pressure for venous return is right atrial pressure. The upstream pressure driving venous return, the mean systemic pressure (P_MS), is the volume-weighted average of pressures throughout the entire systemic vascular network. Because a much larger fraction of the total circulating volume is downstream from the resistance vessels, P_MS is much closer to the right atrial pressure (P_RA) than to MAP (Fig. 1-7). Were the P_RA to rise suddenly to equal the P_MS, all blood flow would stop. Indeed, in an experimental setting, P_MS can be determined by synchronously clamping the aorta and vena cava to stop flow and opening a wide-bore communication between them. Mean systemic pressure is influenced by the circulating blood volume and vascular capacitance, which in turn is a function of vascular tone. Thus, P_MS rises under conditions of hypervolemia, polycythemia, and right-sided CHF; it declines during abrupt vasodilation, sepsis, hemorrhage, and diuresis. Up to a certain point, lowering P_RA while preserving P_MS increases driving pressure and improves venous return. However, when P_RA is reduced below the surrounding tissue pressure, the thin-walled vena cava collapses near the thoracic inlet. Effective downstream pressure for venous return then becomes the pressure just upstream to the point of collapse, rather than the P_RA.
FIGURE 1-6. Interaction of Frank-Starling and venous return (VR) curves. With normal heart function, observed cardiac output is determined by such vascular factors as filling status ($A \rightarrow B$) and vasoconstriction ($C$). Sympathetic stimulation and heart failure have opposing effects on the Starling curve and cardiac output. The upstream mean systemic pressure (MSP) that drives venous return is a hypothetical point determined by extrapolating the venous return curve to the venous pressure axis where all cardiac output ceases. Note that VR improves linearly as CVP falls—up to the point at which central vessels collapse.
FIGURE 1-7. Forces driving the systemic circulation. The mean systemic circulatory pressure is the weighted average of arterial, capillary, and venous pressures and equals the blood pressure at any point with the circulation stopped. It is much closer to venous than to mean arterial pressure because of the large venous capacitance bed. MSP minus $P_{RA}$ is the driving pressure for venous return.
At any given moment, the cardiac output is determined by the intersection of the venous return curve and the Starling curve. In the analysis of a depressed cardiac output, both aspects of circulatory control must be considered. For example, when positive end-expiratory pressure (PEEP) is applied, \( P_{RA} \) rises, inhibiting the venous return. However, \( P_{MS} \) rises simultaneously, and compensatory vascular reflexes are called into action to reduce the venous capacitance and expand the circulating volume. Therefore, unlike patients with depressed vascular reflexes or hypovolemia, most healthy individuals do not experience a reduction of cardiac output under the influence of moderate PEEP. Although an increase in venous resistance can also reduce the venous return, it is uncommon for the venous resistance to increase without an offsetting change in \( P_{MS} \). However, positional compression of the inferior vena cava by an intra-abdominal mass (e.g., during advanced pregnancy) may account for postural changes in cardiac output in such patients.

**Capillary Fluid Filtration and Tendency for Tissue Edema**

Classical concepts first developed by Starling and later modified to improve accuracy and clinical relevance indicate that fluid transport at the tissue level is normally determined by the hydrostatic and osmotic pressure differences between the capillary (\( P_{CAP}, \Pi_{CAP} \)) and interstitial (\( P_{IF}, \Pi_{IF} \)) compartments (Fig. 1-8, left). Rising hydrostatic pressure and depression of oncotic pressure favor edema formation, whereas the opposites favor its prevention or resolution. The capillary filtration coefficient (\( C_F \)), which increases with acute inflammation, characterizes the ease or difficulty with which any such differences cause a net shift between compartments. Expressed in equation form:
This relationship, though admittedly simplified, serves to indicate that increased interstitial fluid (edema) may form because of an increase in venous and capillary pressures, a fall in serum oncotic pressure, or increased number and leakiness of the capillary pores. All three are potential targets for clinical intervention (Fig. 1-8, right).

CHARACTERISTICS OF THE DISEASED CIRCULATION

Left Ventricular Insufficiency

Congestive Heart Failure

Diagnostics

The term “heart failure” (or CHF) is often loosely applied to conditions in which the filling pressures of the left heart are increased sufficiently to cause dyspnea or weakness at rest or mild exertion. Congestive symptoms can develop when systolic cardiac function is preserved (volume overload, renal insufficiency, diastolic dysfunction, RV encroachment, and pericardial effusion), as well as during myocardial failure itself. Unlike the normal LV, which is relatively sensitive to changes in its preload and insensitive to changes in its afterload, the failing LV has the opposite characteristics (see Fig. 1-2). Changes in afterload can therefore make a major difference in LV systolic performance, whereas preload manipulation usually elicits little benefit, unless it reduces afterload indirectly by shrinking chamber volume and wall tension. Wide QRS complexes characterize the ventricular asynchrony of bundle branch block, and in certain patients with such conduction delays, resynchronization by biventricular pacing may improve left ventricular (LV) filling time, reduce mitral regurgitation, and lessen dyskinesis. Together, these benefits often improve contractile efficiency impressively.

Radiographic evidence of acute heart failure includes perivascular cuffing, a widened vascular pedicle, blurring of the hilar vasculature, and diffuse infiltrates that tend to spare the costophrenic angles. Unlike pneumonia and acute respiratory distress syndrome (ARDS), these infiltrates tend to lack air bronchograms and are usually unaccompanied by an acute change in heart size. Chronic CHF is typified by Kerley B lines, dilated cardiac chambers, and increased cardiac dimensions.

The increased stretching of myocardial tissue in response to ventricular overload promotes the release of two endogenous natriuretic peptides: atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). Cardiac natriuretic peptides can lower excessive levels of angiotensin II, aldosterone, and endothelin I (another endogenous vasoconstrictive peptide) thus inducing a variety of beneficial effects—arterial and venous vasodilation, enhanced diuresis, and inhibition of sodium reabsorption.

ANP is stored within granules in the atria and ventricles, so even a minor amount of cardiac muscle stretch, such as that resulting from routine exercise, can cause an efflux of this peptide into the circulation. BNP, by contrast, is synthesized within the ventricles, and only minimal amounts are stored in granules. Instead, BNP is synthesized de novo, or as needed, in response to left ventricular wall elongation secondary to myocardial stress (e.g., volume overload). Thus, the BNP compensatory response to myocardial injury usually (but not invariably) indicates ventricular dysfunction or distention. BNP (and the closely related, less quickly degraded N-terminal BNP) levels consistently rise above their normal values in patients with CHF. The diuretic and vasodilating properties of BNP point to a potentially important role for this peptide, not only as a diagnostic tool in CHF but also as a treatment option for well-selected patients (e.g., nesiritide). To date, this therapeutic potential has not been fully realized (see below).
BNP measurements can provide useful information for excluding CHF, indicating its severity, tracking progress, and gauging likely outcome. Unfortunately, BNP is not selective for cardiac filling status, as it also increases in a variety of lung diseases, renal insufficiency, sepsis, and inflammatory states.

When faced with a patient who appears to have pulmonary venous congestion, a number of key questions should be asked in determining its etiology.

1. **Is forward output adequate to perfuse vital tissues?** When perfusion is severely impaired, consideration should be given to mechanical ventilation and invasive hemodynamic monitoring, especially in the setting of coexisting pulmonary venous congestion and lactic acidosis. Reducing tissue $O_2$ demand and correcting disturbances in oxygen content, serum pH, electrolyte balance, and ventricular loading conditions are of prime importance. Inotropic or vasopressor therapy may be indicated for hypotension, whereas hypertensive patients and those with a highly elevated SVR may benefit from vasodilators.

2. **Is there evidence of systolic dysfunction?** Adequate perfusion does not necessarily imply intact systolic function—forward output may be maintained at the cost of high preloading pressures and pulmonary vascular congestion. If perfusion is adequate and systolic function of cardiac valves and myocardium remains intact, the patient may simply be volume overloaded or manifesting diastolic dysfunction. Echocardiography helps greatly in this assessment.

3. **What is the LV size?** LV chamber dilation usually indicates a chronic process—most commonly long-standing ischemic heart disease, cardiomyopathy, or LV diastolic overload (aortic or mitral valvular insufficiency). Therapy in such cases should be directed at optimizing afterload (with systemic vasodilators) or at improving myocardial oxygen supply (coronary vasodilators). If there is excessive inspiratory effort, mechanical ventilation can reduce both $O_2$ demand and left ventricular afterload by raising inspiratory and mean pleural pressures. If left ventricular cavity size is normal, mitral stenosis, tamponade, constrictive pericarditis, acute myocardial infarction, hypertrophic cardiomyopathy, or diastolic dysfunction should be suspected. Left ventricular wall hypertrophy, myocardial infiltration, or interdependence with a swollen RV may limit stroke volume and cardiac output, despite normal contractility. A distended left atrium sometimes provides a clue in such cases.

4. **Does the LV show global or regional hypokinesis?** Regional hypokinesis/dyskinesis suggests localized disease (e.g., ischemia or infarction). Stress cardiomyopathy (Takotsubo) may temporarily show the signature findings of apical ballooning with preserved basilar contraction. Echocardiography and precordial electrocardiography (ECG) are instrumental in this assessment. Generalized hypokinesis of a heart with normal chamber size often reflects the stunned myocardium of trauma, diffuse ischemia, drug overdose, toxin ingestion, or post-tachycardia dysfunction.

5. **Is there evidence for valvular dysfunction?** Aortic stenosis may depress cardiac output by causing excessive afterload, myocardial ischemia, or hypertrophic impairment of ventricular filling. Mitral regurgitation impairs forward output and produces congestive symptoms by allowing partial retrograde venting of the ejected volume. Acute chamber enlargement (regardless of cause) may worsen congestive symptoms by producing transient mitral regurgitation because of papillary muscle dysfunction or mitral ring dilation.

6. **Is there evidence for increased pulmonary vascular permeability or hypoalbuminemia?** The tendency to form pulmonary edema relates not only to hydrostatic pressure but also to the plasma oncotic pressure and pulmonary capillary permeability. Hence, edema may form at a relatively low pulmonary venous pressure if oncotic pressure is reduced or the microvascular endothelium is leaky (ARDS). Conversely, the lungs may remain relatively dry despite high left heart filling pressures when enlarged lymphatic drainage channels with
greater capacity have had time to develop (e.g., mitral stenosis). Kerley lines are the radiographic signatures of lymphatic dilation.

The physical examination should be directed toward the detection of hypoperfusion (reduced mental status, oliguria) and compensatory vasoconstriction (reduced skin temperature, prolonged capillary filling time, etc.). Rales (crackles) are often difficult to detect in bedridden patients who breathe shallowly and in those receiving mechanical ventilatory support. Auscultation of gravitationally dependent regions is mandatory. The chest X-ray (CXR) provides key information regarding heart size, vascular distribution, pulmonary infiltrates, and pleural effusions. Computed tomography using reconstructive imaging techniques is informative in questionable cases—as when the chest wall interferes with CXR interpretation. Echocardiography and radionuclide ventriculography provide important information regarding chamber size, contractility, diastolic filling, valvular function, $P_{RA}$, pericardial volume, and filling status of the central pulmonary veins. Although transesophageal echocardiography is not always feasible to perform, the detail it provides is generally superior to its transthoracic counterpart, especially in patients with obstructive lung disease or massive obesity.

**Therapeutics**

As a general rule, the therapy of CHF should be geared to document pathophysiology. Reversal of abrupt-onset tachycardias and arrhythmias is frequently the key to relieving congestion, especially in patients with valve dysfunction, or stiff or ischemic hearts. Whereas diuretics help in most cases, inotropic and vasoactive agents should be reserved for documented disorders of myocardial function refractory to adjustments of filling pressure, pH, and electrolytes. Angiotensin-converting enzyme (ACE) inhibitors (e.g., captopril, enalapril) and/or systemic vasodilators should be used when an elevated SVR and/or valvular insufficiency are documented in the setting of adequate preload and blood pressure. Nitrates may aid cardiac ischemia but can precipitate hypotension in patients with borderline or inadequate filling pressures. New-onset atrial or ventricular arrhythmias or conduction disturbances (e.g., atrial fibrillation, atrial flutter, heart block) should be treated aggressively if they reduce forward output or cause pulmonary edema (see Chapter 4).

Although calcium channel blockers can benefit congestive failure by controlling hypertension, slowing tachycardia, or reversing coronary spasm, they should only be used in well-selected patients; these agents depress cardiac contractility and may impair conduction. In similar fashion, β-Blockers reduce myocardial oxygen consumption by decreasing the heart rate and contractility but have the potential to precipitate CHF, conduction system disturbances, or bronchospasm. β-Adrenergic blockade should be reserved for cases of documented ischemia or other firm indications (e.g., thyroid storm, delirium tremens, uncontrolled supraventricular tachycardia). They should not be considered first-line measures in other acute forms of CHF.

Nesiritide, hBNP, a 32-amino acid recombinant human BNP, represents a unique treatment for acutely decompensated CHF (ADHF) and was the first drug introduced in its class. hBNP has been approved for the IV treatment of patients with ADHF who have dyspnea at rest or with minimal exertion. hBNP has been shown to exert potent vasodilatory effects and to effect significant diuresis and natriuresis in patients with severe CHF. In patients with ADHF, hBNP also has been shown to significantly decrease plasma norepinephrine and aldosterone levels, as well as cardiac preload and vascular resistance, without stimulating the changes in heart rate seen with inotropic agents. When added to standard therapy in the treatment of ADHF, hBNP improves hemodynamic function to a significantly greater extent than nitroglycerin (see Chapter 3). Its use has become somewhat controversial, however, as it may cause profound hypotension, bradycardia, and renal dysfunction in some patients.

Another promising class of noncatecholamine-based agents is the calcium sensitizers. The initial representative of this category is levosimendan, a drug that is marketed but yet to be deployed on a wide scale (see Chapter 3).
It has distinct inotropic and vasodilating properties and must be used only with particular caution in patients who have severely impaired kidney or liver function and in those who are hypotensive and tachycardic.

**Right Ventricular Dysfunction**

Certain disease conditions account for the great majority of acute problems arising primarily from RV dysfunction: RV ischemia and infarction; cor pulmonale complicating parenchymal, vascular, or hypoventilatory hypoxemic lung diseases (e.g., sleep apnea); and ARDS.

**Right Ventricular Infarction**

The RV receives the majority of its blood supply from the right coronary artery. It is not surprising, therefore, that RV infarction complicates as many as 30% of inferior myocardial infarctions, as well as a smaller percentage of anterior infarctions. The diagnosis should be suspected when there are signs of systemic venous hypertension, an unimpressive or clear CXR, and evidence of ST segment elevation or Q waves over the right precordium (V$_4$R). A suggestive enzyme profile confirms the diagnosis. In the initial phase of management, RV infarctions typically demand aggressive administration of intravenous fluids to sustain optimal blood pressure and cardiac output. The LV may be required to take up the work of pumping blood through both the systemic circuit (directly) and the pulmonary circuit (indirectly), using ventricular interdependence. Dilatation of the RV and fluid loading tighten these linkages by crowding the two ventricles within the pericardial sac, stretching shared circumferential muscle fibers, and shifting the mobile interventricular septum. Recovery from, accommodation to, or compensation for RV infarction tends to occur over several days. If cardiac output can be supported during this interval, the outlook for patients without other cardiopulmonary diseases is generally good. Prognosis depends not only on the size of the infarction but also on the presence or absence of increased PVR.

**Cor Pulmonale**

**Pathogenesis**

In its purest form, cor pulmonale (see Chapter 21) is defined as hypertrophy, dilatation, or failure of the RV in response to excessive PVR. By definition, this term excludes cardiomyopathy or secondary changes in RV function resulting from pulmonary venous hypertension or LV failure. Three reinforcing causes of pulmonary hypertension are a restricted capillary bed, alveolar hypoxia, and acidosis. Although extensive obliteration, occlusion, constriction, or compression of the capillary bed may be the underlying cause, increased cardiac output and superimposed hypoxemia or acidosis may dramatically elevate pulmonary arterial pressure ($P_{PA}$). The normal RV cannot sustain adequate forward output at mean pulmonary arterial pressures that exceed approximately 35 mm Hg. Given sufficient time, however, the RV wall can thicken sufficiently to generate pressures that rival those in the systemic circuit. Arterial smooth muscle also hypertrophies over time, intensifying the response to alveolar hypoxemia and pharmacologic vasoconstrictors. Most diffuse pulmonary insults can raise the PVR enough to decompensate an already compromised RV. Massive pulmonary embolism is the most common cause of acute cor pulmonale in a patient without prior cardiopulmonary abnormality. In mechanically ventilated patients, lung overdistention with attendant capillary compression may markedly accentuate RV loading.

Chronic cor pulmonale can result from severe lung disease of virtually any etiology (especially those that obliterate pulmonary capillaries and induce chronic hypoxemia). Acutely decompensated cor pulmonale occurs frequently in patients with chronic obstructive pulmonary disease (COPD). In such patients, RV afterload can fall dramatically with correction of bronchospasm, hypoxemia, and acidosis. Because about one half of the normal pulmonary capillary bed can be obstructed without raising the resting mean $P_{PA}$ significantly above the normal
range, pulmonary hypertension in a normoxemic person at rest usually signifies an important reduction in the number of patent pulmonary capillaries. After the capillary reserve has been exhausted, \( P_{PA} \) varies markedly with cardiac output. Thus, in a predisposed patient, elevations of baseline pulmonary arterial pressure often signify variations in cardiac output, rather than worsening of lung pathology.

**Diagnosis**

The measurement of central venous pressure (CVP), pulmonary artery occlusion ("wedge") pressure (\( P_w \)), and the computation of PVR help separate right from left heart disease. Echocardiography is an invaluable diagnostic adjunct, often allowing estimation of pulmonary arterial pressure as well as providing detailed anatomical information regarding the dimensions and functions of the two ventricles. The physical findings of acute cor pulmonale are those of pulmonary hypertension: hypoperfusion, RV gallop, and a loud \( P_2 \).

Pulsatile hepatomegaly, systemic venous congestion, a parasternal lift, and peripheral edema strongly implicate RV failure and severe pulmonary hypertension. Deep breathing may accentuate these right heart findings, as inspiratory increases of blood flow returning to the thorax raise \( P_{PA} \) and stress the compromised RV. Unfortunately, many of these signs are difficult to elicit in patients with hyperinflated or noisy lungs.

**Ancillary Diagnostic Tests**

Radiographic signs of pulmonary arterial hypertension include dilated, sharply tapering central pulmonary arteries with peripheral vascular "pruning." Although precise measurements are often difficult to make, a right lower lobar artery dimension greater than 18 mm diameter (on the standard PA film) or main pulmonary arteries greater than 25 mm in diameter (judged on lateral) strongly suggest subacute or chronic pulmonary hypertension. Overall heart size may appear normal until disease is advanced, especially in patients with hyperinflation. Encroachment of the RV on the retrosternal airspace in the lateral view is an early but nonspecific sign. When renal function allows, the contrast-enhanced computed tomography (CT) scan of the thorax confirms RV dilatation. Catheter-based techniques allow computation of RV volume and/or RV ejection fraction. Beat-by-beat analysis of the thermodilution temperature profile allows both to be assessed, whereas a double indicator (dye/thermodilution) method permits determination of these indices as well as central blood volume, stroke work, lung water, and others.

ECG criteria for RV hypertrophy are insensitive and nonspecific. In acute cor pulmonale, changes characteristic of hypertrophy are lacking. \( P \) pulmonale and a progressive decrease in the \( R/S \) ratio across the precordium are sensitive but nonspecific signs. Conversely, the \( S_1, Q_3, T_3 \) pattern, right axis deviation greater than 110 degrees, \( R/S \) ratio in \( V_5 \) or \( V_6 \) less than 1.0, and a QR pattern in \( V_1 \) are relatively specific but insensitive signs.

Radionuclide ventriculography and echocardiography more reliably document RV and LV functions noninvasively. In patients with true cor pulmonale, LV systolic function should remain unaffected.

**Management of Acute Cor Pulmonale**

The key directives in managing cor pulmonale are to maintain adequate RV filling and perfusion, to reverse hypoxemia and acidosis, to establish a coordinated cardiac rhythm, reverse atelectasis, and treat the underlying illness. The majority of patients with decompensated COPD and cor pulmonale have a reversible hypoxemic component. Although oxygen must be administered cautiously, patients with baseline CO\(_2\) retention should not be denied \( O_2 \) therapy. Acidosis accentuates the effect of hypoxemia on PVR, whereas hypercarbia without acidosis exerts less effect. This should be borne in mind when deciding the advisability of buffering pH in permissive hypercapnia.
Bronchospasm, infection, and retained secretions must be addressed. When extreme polycythemia complicates chronic hypoxemia, careful lowering of the hematocrit to approximately 55% may significantly reduce blood viscosity, decrease RV afterload, and improve myocardial perfusion. To improve blood viscosity, it helps to rewarm a profoundly hypothermic patient.

The effects of digitalis, inotropes, and diuretics in acute cor pulmonale are variable; these drugs should be employed cautiously. Gentle diuresis helps relieve symptomatic congestion of the lower extremities, gut, and portal circulation. Diuresis may reduce RV distention and myocardial tension, improving both its afterload and perfusion. Any depression of cardiac output resulting from diuresis may also cause a secondary reduction of $P_{PA}$.

In patients requiring RV distention and ventricular interdependence to sustain adequate stroke volume, vigorous diuresis or phlebotomy (now seldom practiced) may have adverse consequences. Central vascular pressures, therefore, should be carefully monitored. The effects of cardiotonic agents in the treatment of acute cor pulmonale are also unpredictable. Digitalis has only a small inotropic effect on the performance of a nonhypertrophied RV but may be helpful in chronic cor pulmonale. Though slow to take effect, digoxin often proves useful in controlling rapid heart rate in atrial fibrillation without depressing myocardial function. Inotropes such as dopamine and dobutamine can improve left ventricular function and boost the perfusion pressure of the RV. Furthermore, because the ventricles share the septum and circumferential muscle fibers, it is likely that improved left ventricular contraction benefits the RV through systolic ventricular interdependence. Associated arrhythmias and conduction disturbances, however, may disrupt the AV coordination that is so vital to effective RV filling and performance.

For a minority of patients, calcium channel blockers (e.g., nifedipine, diltiazem, amlodipine) reduce PVR and boost cardiac output by decreasing RV afterload. This effect, however, is highly variable; these drugs may also depress myocardial function and/or reduce coronary perfusion pressure. Evaluation of response is best conducted cautiously during formal cardiac catheterization before they are prescribed. For patients with a clearly reversible component to the pulmonary hypertension, inhaled nitric oxide (or aerosolized prostanycin [Flolan]) may prove to be a useful bridge to definitive therapy or physiologic adaptation. Unfortunately, tolerance to nitric oxide rapidly develops and in itself does not provide a long-term solution. For patients with severe ongoing pulmonary hypertension, anticoagulation is thought advisable. Several therapies recently released into clinical practice hold promise for chronic use in some patients with reactive pulmonary vasculature. These include epoprostenol, treprostinil, bosentan, and sildenafil and their derivatives.

**Acute Respiratory Failure**

**Mechanisms of Circulatory Impairment in ARDS**

Although cardiac output usually increases during the early stage of ARDS in response to the precipitating stress or in compensation for hypoxemia, this is less often true when the illness is far advanced. The performance of one or both ventricles may deteriorate as the lung disease worsens, compounding the problem of inadequate tissue $O_2$ delivery. The cardiac dysfunction that accompanies advanced respiratory failure is incompletely understood. Effective preload may be reduced by PEEP, third spacing, capillary leakage, and myocardial stiffening secondary to ischemia or catecholamine stimulation. Contractility of either ventricle may be impaired by hypotension, ischemia, electrolyte abnormalities, or cardiodepressant factors released during sepsis, injury, or other inflammatory condition. Compression, obliteration, and hypoxic vasoconstriction of the pulmonary vasculature impede ejection of the afterload-sensitive RV, a low pressure-high capacity pump. Increased wall tension also tends to diminish RV perfusion. Severe pulmonary hypertension is an ominous sign in the later stages of ARDS.

**Assessing Perfusion Adequacy**
The assessment of perfusion adequacy in ARDS is addressed in detail elsewhere (see “Oxygenation Failure,” Chapter 24). However, a few points deserve emphasis here. Individual organs vary widely with regard to O₂ demand, completeness of O₂ extraction, and adaptability to ischemia or hypoxia. Cerebral and cardiac tissues are especially vulnerable to hypoxemia. In these organs, the O₂ requirement per gram of tissue is high, O₂ stores are minimal, and O₂ extraction is relatively complete—even under normal circumstances. Subtle changes in mental status may be the first indication of hypoxemia, but the multiplicity of potential causes (e.g., early sepsis, dehydration, anxiety, sleep deprivation, drug effects) renders disorientation and lethargy difficult to interpret. Although cool, moist skin often provides a valuable clue to inadequate vital organ perfusion, vasopressors, and disorders of vasoregulation common to the critically ill patient reduce the utility of this finding.

The kidney usually provides a window on the adequacy of vital organ perfusion through variation of its urine output, pH, and electrolyte composition. Adequate urine volume and sodium and bicarbonate excretion suggest sufficient renal blood flow when the kidneys are normally functioning. Unfortunately, rather than reflecting the adequacy of perfusion, variations in urine volume and alterations of urine composition are often due to drug effects, diurnal variations, and or glomerular or tubular dysfunction. As sustained hypoperfusion activates anaerobic metabolic pathways, arterial pH and bicarbonate concentrations decline and lactic acid levels rise, widening the anion gap. Although adequacy of cardiac output can seldom be determined unequivocally by any single calculated index, analysis of the O₂ contents of arterial and mixed venous blood is valuable when addressing questions of tissue O₂ supply and utilization. In recent years, near-infrared spectrophotometry, gastric mucosal pH, and sublingual PCO₂ have been investigated as markers of insufficient O₂ delivery to vital organs. Despite the potential value of such indices, inadequacy of systemic O₂ delivery is perhaps best judged from a battery of indicators, including the clinical examination of perfusion-sensitive organ systems (urine output and composition, mental status, ECG, etc.), the cardiac index, SVR, the presence or absence of anion gap acidosis, lactate levels and trends, the mixed venous oxygen saturation (SvO₂), and the calculated O₂ extraction.

Table 1-3. Causes of Pericarditis

<table>
<thead>
<tr>
<th>Infections</th>
<th>Dissecting Aneurysm</th>
<th>Malignancy</th>
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<tbody>
<tr>
<td>Viral</td>
<td>Rheumatologic diseases</td>
<td>Trauma</td>
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<td>TB</td>
<td>Dresser syndrome</td>
<td>Uremia</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Anticoagulation</td>
<td>Radiation</td>
</tr>
<tr>
<td>Fungal</td>
<td>Myocardial infarction</td>
<td>Drugs</td>
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Improving Perfusion Adequacy in ARDS

Apart from efforts to improve cardiac output and arterial O₂ content (e.g., reversal of profound anemia, inotropic, or vasoactive drugs), tissue oxygenation and perfusion may be enhanced by reducing metabolic demand. Metabolic needs (and perfusion requirements) may be decreased impressively by controlling sepsis and fever,
alleviating anxiety and agitation, and providing assistance (O₂, bronchodilators, ventilatory support) to reduce the work of breathing. Therapy directed at improving cardiac output in the setting of ARDS should be guided by assessing the heart rate, contractility, and the loading conditions of each ventricle independently. Minor elevations of pulmonary venous pressure exacerbate edema, necessitating higher levels of PEEP, mean airway pressure, and supplemental O₂. Attempts should be made to reduce RV afterload by correcting hypoxemia and acidosis. Although a certain minimum level of PEEP must be maintained in the early phase of ARDS to avoid ventilator-induced lung damage, unnecessary elevations of mean airway pressure may overdistend patent lung units, thereby compressing alveolar capillaries and accentuating the impedance to RV ejection. Prone positioning may be a very helpful alternative.

Pericardial Constriction and Tamponade
The pericardium normally supports the heart, shields it from damage or infection, enhances diastolic ventricular coupling, and prevents excessive acute dilatation of the heart. In the intensive care unit (ICU), three types of pericardial disease are noteworthy: acute pericarditis, pericardial tamponade, and constrictive pericarditis.

Acute Pericarditis
Acute pericardial inflammation arises from diverse causes (Table 1-3). The characteristic complaint is chest pain, eased by sitting and leaning forward and aggravated by supine positioning, coughing, deep inspiration, or swallowing. Dyspnea, referred shoulder pain, and sensations of chest or abdominal pressure are frequent. Unless muffled by effusion, pericarditis can usually be detected on physical examination by a single phase or multicomponent friction rub. The rub is often evanescent or recurrent, best heard with the patient leaning forward and easily confused with the crunch of pneumomediastinum, a pleural rub, coarse rhonchi, or an artifact of the stethoscope moving against the skin. Early ECG changes include ST segment elevation, which, unlike the pattern in acute myocardial infarction, is concave upward and typically present in all leads except AVR and V₁. The reciprocal depression pattern of regional infarction is absent. Initially, the T waves are upright in leads with ST segment elevation—another distinction from acute infarction. Depression of the PR segment occurs commonly early in acute pericarditis. The ST segments return to baseline within several days, and the T waves flatten. Tropionins may be mildly elevated. Unlike acute myocardial infarction, ST segments usually normalize before the T waves invert. Eventually, T waves revert to normal, but this process may require weeks or months to complete. Management of uncomplicated pericarditis (without tamponade) includes careful monitoring, treatment of the underlying cause, and judicious use of nonsteroidal antiinflammatory agents for selected cases. Anticoagulation, though not absolutely contraindicated, should be recognized as posing some hazard. Occasionally, pericarditis is complicated by hydraulic cardiac compression (tamponade) or the development of a constricting pericardial sac.

Pericardial Tamponade
Although pericardial fluid tends to reduce pain and discomfort by buffering the friction between the heart and pericardium, the rapid accumulation of pericardial fluid may compress the heart, resulting in tamponade (see Chapter 3). At least 250 mL of fluid must collect before an obviously enlarged heart shadow is noted on the chest roentgenogram; a normal or unchanged chest film does not exclude the presence of a hemodynamically important effusion. Echocardiography is considerably more sensitive but not infallible. Effusions that cause tamponade can be circumferential, asymmetrical, or loculated. In the supine patient, small unloculated effusions pool posteriorly. Common settings include post-op from thoracic surgery, chest trauma, and catheterization or endovascular instrumentation (e.g., misplaced guidewires and/or central venous catheters).

Tamponade physiology classically results in a triad of low arterial pressure, elevated neck veins, and a quiet
precordium, and in its extreme form can produce pulseless electrical activity (PEA). Recumbency intensifies dyspnea, whereas sitting upright tends to relieve it. Although tamponade is properly considered a diagnosis founded on history and physical examination, massive obesity interferes with making a confident diagnosis from physical signs alone. Low QRS complex voltage and some degree of electrical variation are sometimes observed on the ECG tracing, but these classical findings are not reliable. (The ECG does help, however, in ruling out other diagnostic possibilities.) Arterial pressure tracings disclose exaggerated reductions of systolic pressure, a shared characteristic of the conditions that tend to mimic it. These include tension pneumothorax, severe gas trapping (auto-PEEP), massive pulmonary embolism, and cardiogenic shock. Echocardiography helps confirm the diagnosis of tamponade, serving as an invaluable bedside aid in distinguishing among these differential possibilities. Right atrial collapse in the face of distended central veins is a sensitive indicator, but RV collapse is more specific.

As fluid accumulates, nonspecific ECG findings include reduced QRS voltage and T wave flattening. In this setting, electrical alternans suggests the presence of massive effusion and tamponade. Although echocardiographic quantification of effusion size is imprecise, it is the most rapid and widely used technique. Large pericardial effusions (>350 mL) give rise to anterior echo-free spaces and exaggerated cardiac swinging motions. Diastolic collapse of the right heart chambers suggests a critical degree of fluid accumulation and tamponade. Alternative diagnostic techniques include the CT scan with intravenous contrast and the MRI scan (when feasible).

**Physiology of Pericardial Tamponade**

Acute pericardial tamponade is a hemodynamic crisis characterized by increased intracardiac pressures, limitation of ventricular filling throughout diastole, and reduction of stroke volume. Normally, intrapericardial pressure is similar to intrapleural pressure, but less than either right or left ventricular diastolic pressures. Rapid accumulation of pericardial fluid causes sufficient pressure within the sac to compress and equalize right and left atrial pressures, reducing maximal diastolic dimensions and stroke volume. Reflex increases in heart rate and adrenergic tone initially maintain cardiac output. In this setting, any process that quickly reduces venous return or causes bradycardia (e.g., hypoxemia, β-blockade) can precipitate shock.
FIGURE 1-9. Contrast of pericardial constriction and tamponade as reflected in CVP tracings (lower panels). Unlike the venous pressure tracing of constriction, the “Y descent” is attenuated in tamponade because early diastolic filling is impaired. The systolic “X descent” is well preserved in both conditions.

Tamponade alters the dynamics of systemic venous return and cardiac filling (Fig. 1-9). As cardiac volume transiently decreases during ejection, pericardial pressure falls, resulting in a prominent X descent on the venous pressure tracing. Tamponade attenuates the normal early diastolic surge of ventricular filling and abolishes the Y descent (its representation on the venous pressure tracing). Pulsus paradoxus, a result of exaggerated normal physiology, may develop simultaneously. Inspiration is normally accompanied by an increase in the diastolic dimensions of the RV and a small decrease in LV volume. These changes reduce LV ejection volume and systolic pressure (<10 mm Hg) during early inspiration. Pericardial tamponade accentuates this normal fluctuation to produce pulsus paradoxus. With an arterial line in place, paradoxical pulse is easily quantified by noting the respiratory variation of systolic pressure during the end-inspiratory and end-expiratory phases of the ventilatory cycle. Paradoxical pulse can also be detected in traditional fashion by lowering the cuff pressure of a sphygmomanometer slowly from a point 20 mm Hg above systolic pressure until the Korotkoff sounds are heard equally well throughout both inspiration and expiration. The “paradox” is the difference between the pressure at which systolic sound is first audible and the point at which the systolic sound is heard consistently throughout the respiratory cycle. Pulsus paradoxus and certain other hemodynamic manifestations of pericardial tamponade depend on inspiratory augmentation of systemic venous return; as the RV swells, it restricts left ventricular chamber volume. Paradox may be absent in pericardial tamponade if underlying heart disease markedly elevates left ventricular diastolic pressure or if the LV fills by a mechanism independent of respiratory variation (e.g., aortic regurgitation). It may be hard to detect in the presence of tachycardia or arrhythmia.

**Clinical Manifestations of Pericardial Tamponade**

Reduced systemic arterial pressure and pulse volume, systemic venous congestion, and a small, quiet heart comprise the classic presentation of pericardial tamponade. However, other disorders, including obstructive pulmonary disease, restrictive cardiomyopathy, RV infarction, massive pulmonary embolism, and constrictive pericarditis, may also present with systemic venous distention, pulsus paradoxus, and clear lungs. Hyperactivity
of the adrenergic nervous system is evidenced by tachycardia and cold, clammy extremities. The most common physical findings are jugular venous distention and pulsus paradoxus. However, tachypnea may render these signs difficult to elicit. Orthopnea that is not explained by neuromuscular weakness, obstructive lung disease, or pulmonary edema warrants strong consideration of tamponade.

**Laboratory Evaluation**

No feature of the CXR is diagnostic of pericardial tamponade. Electrical (QRS) alternans on the ECG in a patient with a known pericardial effusion is suggestive, but not definitive evidence. Electrical alternans may also occur with constrictive pericarditis, tension pneumothorax, severe myocardial dysfunction, and after myocardial infarction. Adjunctive studies are needed to confirm tamponade physiology. Apart from demonstrating pericardial fluid, the echocardiogram can provide additional clues. These include reduction of the “E to F” slope, brisk posterior motion of the intraventricular septum during inspiration, RV diastolic collapse, prominent “swinging” of the heart, and exaggerated inspiratory increases and expiratory decreases in RV size. Yet, however suggestive they may be, the findings of a single echocardiographic study cannot predict the presence or severity of pericardial tamponade. Cardiac catheterization confirms the diagnosis, quantifies the magnitude of hemodynamic compromise, and uncovers coexisting hemodynamic problems. Catheterization typically demonstrates an elevated $P_{RA}$ with a prominent systolic X descent and diminutive or absent Y descent (Fig. 1-9). There is elevation and diastolic equilibration of intrapericardial, RV, and left ventricular pressures (“equalization”). RV diastolic pressures lack the “dip and plateau” configuration characteristic of constrictive pericarditis.

**Management**

In pericardial tamponade, it is essential to maintain adequate filling pressure and heart rate. Peripheral vascular tone must be maintained with pressors, if needed. Volume depletion (e.g., excessive diuresis), hypoxemia, and β-blockade (and other causes of bradycardia) can be life-threatening. As a general rule, fluids should be “wide open” and sinus tachycardia—a compensatory response—left untreated. Intubation of the airway must not be performed unnecessarily and when delay is not prudent, performed only with extreme caution. Positive pressure can further reduce cardiac filling, and vasodilation may drop the central pressures needed for compensation. Because the pressure-volume curve of the distended and liquid-filled pericardial sac is very steep, aspirating 50 to 100 mL of fluid usually leads to a striking reduction in intrapericardial pressure and improvements of systemic arterial pressure and cardiac output. Pericardiocentesis lowers the diastolic pressures in the pericardium, right atrium, RV, and LV and reestablishes normal pressure gradients.

Pericardial fluid can be evacuated by one of three methods: needle pericardiocentesis, pericardiotomy via a subxiphoid window (often under local anesthesia), or pericardiectomy. During pericardiocentesis, the probability of success and the safety of the procedure relate directly to the size of the pericardial effusion. Whereas partial drainage of a massive pericardial effusion may be lifesaving, aspiration of a small pericardial effusion (<200 mL) that is freely mobile within the pericardial sac may be only marginally helpful. A significant hemodynamic effect is also unusual in the absence of a documented anterior effusion, or when loculated clot or fibrin inhibits the free withdrawal of fluid. Pericardiocentesis must not be undertaken by inexperienced personnel or in an inappropriate environment. Needle aspiration should be conducted whenever possible in the cardiac catheterization suite by an experienced cardiologist, using fluoroscopic and needle electrode ECG guidance. Complications include coronary laceration, pneumothorax, myocardial injury, and life-threatening arrhythmias.

Subxiphoid pericardiectomy can be performed safely under local anesthesia in certain critically ill patients. Regardless of drainage method, successful relief of tamponade is documented by the fall of intrapericardial pressure to normal, the reduction of elevated $P_{RA}$, separation of right from left heart filling pressures,
augmentation of cardiac output, and disappearance of pulsus paradoxus. After drainage, the majority of patients should be closely monitored for at least 24 hours in the ICU for evidence of recurrent tamponade. Persistent elevation and equilibration of right and left ventricular diastolic pressures after pericardiocentesis or subxiphoid pericardiotomy suggests a component of pericardial constriction. Pericardiectomy may be required in patients with a component of constriction and in those who experience recurrent tamponade despite repeated needle or subxiphoid drainage.

**Constrictive Pericarditis**

Constrictive pericarditis results from a confining pericardial shell that prevents adequate chamber filling. Although both constriction and tamponade are characterized by elevation and equilibration of right and left ventricular diastolic pressures, they can be differentiated by several key hemodynamic features (Table 1-4). Constrictive pericarditis limits filling primarily in late diastole, whereas tamponade affects filling throughout. Whereas constrictive pericarditis may sometimes demonstrate atrial pressure changes reminiscent of tamponade, the RV pressure contour usually shows a prominent dip and plateau (“square root”) configuration. Pericardial constriction can be mimicked by restrictive or ischemic cardiomyopathy: in both conditions, RV and left ventricular diastolic pressures are elevated, SV and cardiac output are depressed, left ventricular end-diastolic volume is normal or decreased, and end-diastolic filling is impaired. Common ECG findings include low QRS voltage, generalized T wave flattening or inversion,

and an atrial abnormality suggestive of P mitrale. Because constrictive pericarditis tends to progress inexorably, surgical intervention is eventually required if the patient is an otherwise appropriate candidate. Hemodynamic and symptomatic improvement is evident in some patients immediately after operation; in others, however, improvement may be delayed for weeks or months.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pericardial Tamponade</th>
<th>Constrictive Pericarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiographic heart “shadow”</td>
<td>↑ or ↑↑</td>
<td>↔ to ↑↑</td>
</tr>
<tr>
<td>Kussmaul sign</td>
<td>Usually absent</td>
<td>Usually present</td>
</tr>
<tr>
<td>Pulsus paradoxus</td>
<td>Very prominent</td>
<td>May be absent</td>
</tr>
<tr>
<td>RV tracing</td>
<td>Prominent X descent</td>
<td>Dip and plateau</td>
</tr>
<tr>
<td>RA tracing</td>
<td>Negligible Y descent</td>
<td>M or W contour</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prominent Y descent</td>
</tr>
<tr>
<td>Pericardial fluid</td>
<td>Always present</td>
<td>May be present</td>
</tr>
<tr>
<td>ECG</td>
<td>Often reduced amplitude</td>
<td>Low QRS</td>
</tr>
<tr>
<td></td>
<td>Alternans possible</td>
<td>T wave depression</td>
</tr>
</tbody>
</table>

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SUGGESTED READINGS


• Key Points

1. As a general principle, therapeutic decisions are usually best guided by dynamic variables and evaluation of integrated patient responses as opposed to static vital signs and vascular pressures interpreted in relation to fixed targets. Such “functional” monitoring has a better chance to gauge fluid responsiveness and adequacy of cardiac output.

2. The complete hemodynamic profile includes ultrasonic, blood gas, lactate, and data from invasive catheterization. Although now used less frequently, the pulmonary artery catheter often provides data of value that cannot otherwise be collected or monitored.

3. Arterial blood pressure monitoring and waveform analysis are an invaluable aid to the management of patients with shock, hemodynamic instability, respiratory compromise, or brain injury and should be strongly considered in those who are in need of frequent BP or arterial blood gas assessment.

4. Before using hemodynamic information derived from catheter measurements, the transducer system must be accurately zeroed and calibrated, usually an automated function. The dynamic pressure response of the catheter-transducer system should be checked by the rapid flush technique (“snap test”).

5. All vascular pressures of interest are influenced to varying degrees by variations in pleural pressure. Respiratory fluctuations of pleural pressure are conditioned by the alveolar pressure transmission fraction: $C_l/(C_l + C_w)$.

6. It is always hazardous to infer the status of a dynamic system from a single number. The monitored “challenge” is a key maneuver in determining hemodynamic reserves. This may involve reversible noninvasive maneuvers (e.g., a change of measurement of respiratory pulse pressure variation during passive breathing, leg lifting) or rapid fluid bolusing. A notable improvement in key target variables (cardiac output, systemic blood pressure) without the development of symptoms or excessive cardiac filling pressures encourages an increase in the rate of fluid administration.

7. A comprehensive hemodynamic profile includes sampling of mixed or central venous blood for $O_2$ saturation, a comparison of central venous and pulmonary artery wedge pressures, and calculations of systemic vascular resistance and pulmonary vascular resistance. Without such information, adequacy of cardiac output and mechanisms of hemodynamic impairment are often difficult to determine.

8. Echocardiogram and ultrasound provide vital data that complement catheterization and physical examination. Wall motion abnormalities, ventricular contractility, chamber dimensions, dynamics of the central veins, diastolic properties, and valve functioning are well evaluated by this noninvasive method. The pulmonary artery (Swan-Ganz) catheter remains an excellent option for well-selected patients whose clinicians understand the physiologic data stream it provides.

CONDITIONAL IMPORTANCE OF MONITORING HEMODYNAMICS AND FLUID STATUS

Restoring normal perfusion to the vital organs is an undeniable objective of resuscitation and management. However, determining the adequacy and functional status of the cardiovascular system that powers the circuit and distributes nutritive blood flow requires evaluation of its multiple components and of tissue responses to fluid
and drug challenges so that culprit variables can be logically addressed. A panel of observations is required, as no simple indicator exists that characterizes vascular filling status, cardiac functioning, and tissue response. Before an overt shock state is established in sepsis, for example, compensatory changes in vascular tone, cardiac contractility, venous capacitance, and heart rate may support mean blood pressure (BP) and mask the need for volume resuscitation.

As a general principle, therapeutic decisions are usually best guided by dynamic variables and evaluation of integrated patient responses as opposed to static vital signs and vascular pressures interpreted in relation to fixed targets. For example, an abnormally low mean systemic BP of 60 mm Hg may appropriately signal inadequate perfusion and the requirement for fluid resuscitation if observed in conjunction with rapid tachycardia, whereas the same pressure with normal heart rate does not necessarily carry the same significance. The primary therapeutic tools at hand for addressing hemodynamic imbalances are vascular volume expansion, inotropes, pressor agents, and reduction of metabolic demand (as with ventilator support). Excesses of any of these interventions, however, have deleterious consequences.

Unguided and indiscriminate administration of fluid has the potential to harm. Sufficient fluid must be provided to fully prime the system; but it should be kept in mind that restoring arterial pressure does not assure appropriate vital organ perfusion. Mean arterial pressure (MAP) may be normalized by modest fluid and vasopressors despite inadequate vascular filling, insufficient regional flows, and ongoing tissue ischemia. The converse is also true; hypotension does not always respond to aggressive fluid administration alone. In fact, indiscriminate fluid loading in hypotensive patients with sepsis increases cardiac output (CO) only half the time. Early catecholamine support of BP is often required to optimize perfusion during fluid resuscitation. Such nuances of requirements and response emphasize that unguided practices regarding fluid management are concerning, as any surplus not eliminated by the kidneys will appear as pulmonary or systemic organ edema. Recent work indicates that significant cumulative excesses of administered fluid are associated with adverse outcomes.

Even appropriate and careful attention to hemodynamics does not guarantee that the targeted tissues will always benefit. Although acute deficiencies of perfusion promote anaerobic metabolism and must be reversed, tissues may eventually conform to continued oxygen privation over time. Moreover, pushing CO and oxygen delivery does not necessarily mean that the mitochondria will be able to take advantage of this increased O₂ supply. Impaired hemodynamics is not always the primary problem in shock states. Perhaps for this reason, reaching normal or even supranormal targets for O₂ delivery does not assure better outcome—perhaps in some cases, quite the opposite. Making judgments regarding interventions must be guided by objective and quantifiable data.

Nutritive blood flow is delivered with energy supplied by the heart, and fundamental principles of physics indicate that the energy per minute expended is the product of flow and pressure. It is logical, then, that the important global indicators of performance are either flow based (CO, stroke volume) or pressure based (systolic, diastolic, mean, and pulse pressures [PPs]). Because vascular resistance changes little over brief periods, variation of the PP may be considered a crude flow indicator, even though the coupling between PP and stroke volume is imprecise. If hydrostatic gradients are taken into account, the arteriovenous differences in pressure across all vascular beds are similar; flows are not because the local resistances differ. Therefore, whether a given pressure and flow profile measured at the macro level is appropriate must be monitored by metabolic responses such as anion gap and lactate (see below). But these, too, are macro-level variables. Although tissue O₂ responses to ischemia-reperfusion challenges (e.g., BP cuff inflation) can be performed at the periphery with the aid of advanced tissue oxygen sensing technologies, what we currently lack at the bedside is micro level are indicators of perfusion adequacy at the levels of the specific vital organs.

Vascular volume expansion, inotropes, vasoactive drugs, and cardiac rhythm control are the interventions
available to augment the performance of the heart. Therefore, when hemodynamics are clearly in need of support, the questions the physician must answer at the bedside are (1) Is there sufficient circulating volume to optimize preload?; (2) Will intervention-enhanced contractility or reduction of afterload boost cardiac performance? (3) Is vasomotor tone increased, normal, or decreased? (4) Are the cardiac rate and rhythm appropriate for output? To make wise decisions, reliable indicators of fluid adequacy, contractility responsiveness, and vascular tone are required. Lacking these, the answers must often be empirically determined. Nonetheless, static measures (such as arterial pressures, venous pressures, heart rate, CO, and vena caval dimensions) as well as the dynamic responses of such “static” measures to physiologic and physician-imposed challenges (“functional monitoring”) can both provide indispensible guidance, particularly with regard to prediction of fluid responsiveness. When linked to echocardiography, venous oxygen saturation, serum lactate, and urinary output measurements, these form the logical core of today’s hemodynamic evaluation.

**STATIC VERSUS DYNAMIC ASSESSMENTS**

Certain physical signs clearly help in the hemodynamic assessment. For a patient not on vasopressors, skin temperature, capillary refill time, and urine flow give indications of output adequacy. Heart rate and pulse volume are nonspecific but qualitatively helpful in assessing performance and adrenergic response. All of these observations from physical examination become somewhat less reliable in the patient already receiving catecholamines in high doses.

Central venous pressure (CVP), wedge pressure, and vena caval diameter by ultrasonography have long been used as indicators of preload status. These static measurements are all helpful when very high or very low, but each is influenced by intrathoracic pressure and loses specificity over the broad mid-ranges that are so frequently encountered in practice. For example, CVP is influenced by right ventricular afterload, compliance, and pleural pressure. An absolute value for CVP that is less than 8 mm Hg when receiving passive mechanical ventilation does suggest that preload reserve is barely adequate, whereas a value greater than 16 mm Hg is reassuring. However, midrange CVP values hold little information in that regard and neither accurately predicts response to a fluid challenge. This same indecisiveness applies to absolute IVC dimensions assessed by ultrasound; a diameter less than 12 mm suggests cardiac underfilling, whereas a dimension greater than 20 mm indicates adequacy. Values in between are not reliably predictive. During spontaneous breathing, the numbers will change, but the same principle holds: extremes of static values are informative, but the usually encountered midrange values are not.

**Value of Dynamic Functional Monitoring**

Although single (static) values of central vascular pressure have limited utility, dynamic changes in these same indicators during passive inflation are useful in predicting fluid volume responsiveness. Arterial pulse pressure, CVP, and IVC dimensions undergo phasic changes with passive positive pressure ventilation to degrees that depend upon the upstream mean systemic venous pressure to compensate. Wide tidal swings of these indicators strongly suggest fluid volume responsiveness unless there are violations of the underlying assumption that intrabreath variations of pleural pressure and preload account entirely for the observed fluctuation. Utility therefore depends on a large enough tidal swing of pleural pressure, the absence of spontaneous breathing effort, right ventricular failure, cardiac arrhythmia (variable diastolic filling), and intra-abdominal hypertension. During arrhythmia and/or spontaneous breathing, functional monitoring can still be usefully undertaken with an appropriately performed leg lift maneuver (see below).
ARTERIAL BLOOD PRESSURE MONITORING

Noninvasive Arterial Pressure Monitoring

Sphygmomanometer pressures are notoriously inaccurate when cuff width is less than two thirds of arm circumference. Spurious elevations of BP occur when measurements are made with an inappropriately narrow cuff and when arteriosclerosis prevents the brachial artery from collapsing under pressure. Conversely, because tight proximal occlusions can artifactually lower the BP, BP should initially be checked in both arms. It is always wise to compare readings obtained from an arterial line with a cuff pressure periodically and whenever the monitored number disagrees with the clinical impression. In many hypotensive patients with low CO, the “muffle” and disappearance points of diastolic pressure are poorly audible. In profound shock, all Korotkoff sounds may be lost. In this setting, Doppler ultrasonography may detect systolic pressures below the audible range.

Arterial Pressure Waveform

Normally, MAP is similar in all large arterial vessels of a supine subject; there is only a slight pressure gradient between aortic and radial vessels. Posture-related hydrostatic increases of pressure are shared equally between arteries and veins, so that perfusion pressure is little affected. Although MAP is largely the same throughout the arterial tree, waveform contours differ with the caliber of the arterial vessel in question. Peak systolic pressure actually rises in the periphery because of wave reflection. When a vessel is totally occluded by a monitoring catheter, wave reflection may amplify pressure fluctuations to produce sharp spikes of systolic arterial pressure, usually easy to suspect from tracing distortion (Fig. 2-1). The ability of any specific gradient between arterial and venous pressures to perfuse tissue depends directly on the resistance of the vascular bed. An MAP of 65 mm Hg may produce relatively luxuriant flow through dilated vascular beds, whereas an MAP of 100 mm Hg may be inadequate during accelerated hypertension.

FIGURE 2-1. Artifactual elevation of systolic arterial pressure. An underdamped arterial pressure tracing amplified by reflection within an occluded artery may exaggerate the systolic pressure as well as any mean pressure computed from the raw “systolic” and diastolic pressure values.

Depending on the shape of the arterial pressure waveform, the peak systolic \( P_S \) and nadir diastolic \( P_D \)
pressures contribute to varying degrees to MAP. At normal heart rates (60 to 100 beats/min), MAP \( \approx P_D + \frac{1}{3} (P_S - P_D) \). Because its duration is generally longer, the diastolic pressure is the most important contributor to MAP. During tachycardia, \( P_S \) contributes relatively more, and during bradycardia, \( P_S \) contributes relatively less. The arterial pressure waveform changes its contour as well as its precise systolic, diastolic, and (to a lesser extent) mean values, depending on where the arterial system is accessed (Fig. 2-2).

**FIGURE 2-2. Site-specific contours of the arterial pressure waveform.** Note that mean arterial pressure is highest at the aortic root.

**Arterial Waveform Analysis for Cardiac Output Estimation**

It is important to remember that pressure imperfectly indexes flow: unlike pressure, flow is approximately continuous—not pulsatile—and depends on vascular resistance. However, though not appropriate for patients with irregular rhythms and shock states, monitoring devices that analyze the shape of the arterial pressure waveform do a creditable job during sinus rhythm of tracking and trending the CO. Their value is seriously compromised by atrial fibrillation and other chaotic arrhythmias. Although imperfect, analytics of the pressure tracing can yield important information regarding variations in arterial flow as well as the pressure driving it through the circulation. Moreover, it affords an opportunity to evaluate stroke volume variation (SV), a parameter that may be used in conjunction with pulse pressure variation (PPV) to indicate tone in the large arteries: pulse pressure variation (\( \% \)) = \( 100 \times \frac{[\text{PPmax} - \text{PPmin}]}{([\text{PPmax} + \text{PPmin}]/2) \}. \) A similar equation defines SV variation (\( \% \)) = \( 100 \times \frac{[\text{SVmax} - \text{SVmin}]}{([\text{SVmax} + \text{SVmin}]/2) \}. \) PPV/SVV changes in proportion to vascular
Simplified Functional Hemodynamic Monitoring

Useful classification of hemodynamic compromise can be attempted using a few simple bedside observations that determine MAP and reflect stroke volume. The arterial pressure waveform is central to such an analysis, in that, it provides the MAP and the SVV during passive respiration that reflects intravascular volume (Fig. 2-3). A greater than 12% change of PP with passive respiration suggests the need for additional preload. PPV (%) = 100 × \( \frac{[PP_{max} - PP_{min}]}{[PP_{max} + PP_{min}/2]} \). It must be borne in mind, however, that arrhythmias, active breathing, and small tidal volume excursions negate the value of PPV. With this proviso, combining an evaluation of MAP and variation of PP can yield an insight into the type of therapy indicated. A low MAP combined with a low stroke volume (as indicated by wide PPV) strongly suggests hypovolemia, hemorrhage, heart failure, or tamponade. A low MAP combined with negligible PPV is more compatible with sepsis. The responses of these indices to a reversible volume challenge intervention (such as lifting the legs with the upper torso horizontal) can also help to identify the appropriate therapeutic approach (see Passive Leg Raising, below).
FIGURE 2-3. Changes in pulse pressure variation with respiration in a passively ventilated subject. The relatively large difference in pulse pressure during different phases of the ventilation cycle suggests relative underfilling of the vasculature.

Invasive Arterial Pressure Monitoring

Indications
The decision to initiate invasive arterial monitoring must be undertaken cautiously. Many critically ill patients can be adequately monitored by intermittent sphygmomanometry (manual or automated) in combination with the physical examination. However, patients with hemodynamic instability or shock, malignant hypertension, or failure to oxygenate are most likely to benefit from arterial cannulation. A well-adjusted catheter system provides accurate pressure information necessary for hemodynamic monitoring and facilitates blood sampling.

Although convenient and usually reliable, indwelling arterial catheters occasionally give misleading information—especially when the radial artery has been cannulated for an extended time. Errors are most likely to arise in patients who are elderly, are hypotensive, or have underlying vascular disease. Attempts should be made at least once daily to confirm the line pressure by sphygmomanometry. This is especially important in patients receiving vasoactive drugs regulated by radial line pressures. Consideration should be given to measuring femoral pressure when the cuff-derived value and clinical impression disagree seriously with the recorded value.

Complications
Serious complications can arise because of local hemorrhage, infection, and thrombosis. For this reason, the radial artery of the nondominant arm should be used whenever possible. Although common, regional thrombosis of the radial artery seldom results in tissue-damaging ischemia; digital embolization is the greater hazard. Large catheter size, low CO, preexisting arteriopathy, absence of collateral ulnar perfusion, vasopressors, and small wrist circumference increase the risk. (Normal artery caliber tends to parallel the wrist size.)

The Allen test is performed by raising the wrist well above the heart level and compressing the radial and ulnar arteries simultaneously for 10 seconds, blanching the capillary bed. When the ulnar artery is then released, flushing should occur within a few seconds. Not all patients in shock can be tested in this fashion, as sluggish flow may falsely suggest a high risk when none exists. Conversely, although a positive Allen test is reassuring, it does not preclude the development of ischemic damage following radial artery thrombosis. A 20-gauge Teflon catheter is preferred for arterial measurements and sampling because it facilitates insertion, minimizes the risk of thrombosis, and promotes adequate dynamic frequency response. Larger catheters occlude the vessel, creating standing waves, whereas smaller-gauge catheters tend to kink or clot off. Rarely, the arterial catheter may erode the vessel wall to cause aneurysm, localized hematoma, compressive neuropathy, or arteriovenous fistula. Although local colonization is very common, serious soft tissue infections are rare during percutaneous cannulation if the puncture site is kept
sterile, the catheter is used for only a few days, and precautions are taken during blood sampling to preserve sterility. Femoral catheters and “cutdowns” are more likely to become infected. The radial artery is not an appropriate site for injection of any drug. Intra-arterial injections of certain drugs, particularly calcium channel blockers and vasopressors, can cause ischemic necrosis of the hand, a functionally devastating injury. Prolonged, high-pressure flushing can potentially drive clot or gas bubbles retrograde, with risk of (rarely) producing cerebral embolism.

DATA FROM VASCULAR CATHETERS

Concern for the performance or stability of the cardiorespiratory system helps define the need for intensive care. Reliable data relevant to the heart and vasculature are instrumental in diagnosing problems, in selecting and regulating therapy, and in timing interventions. Yet, interpreting the complex relationships among vascular pressures and flows is often complicated by spontaneous fluctuations in metabolism and by variations of the respiratory pressures that influence them. Relatively few clinicians become expert in data interpretation. Balloon flotation pulmonary artery (PA) catheters have been relegated to a secondary status with the recognition that echocardiography (ECHO), noninvasive CO monitoring (e.g., arterial waveform analyzers), and information from CVP catheters—conventional and specially modified—suffice for most purposes. Yet, the PA catheter provides data of clinical value that cannot be obtained otherwise (e.g., pulmonary venous [wedge] pressure and true mixed venous oxygen saturation). Moreover, because the PA catheter incorporates the CVP and requires similar insertion principles, it serves as an appropriate focal point for discussion.

Inserting the Balloon Flotation Catheter

Although detailed descriptions and video demonstrations of insertion technique for the balloon flotation catheter are available elsewhere, a few points are worth emphasizing here. In patients with bleeding disorders, the physician should select a site conducive to applying direct pressure. As opposed to the subclavian and femoral sites, the internal jugular approach tends to be the simplest and least fraught with complications. The right side provides more direct and reliable access to the superior vena cava (SVC) than the left, but either approach can be used effectively. For puncture of the internal jugular or subclavian veins, insertion must be accomplished with the patient supine or even in the Trendelenburg position to ensure vessel distention and minimize the risk of air embolism. In a dyspneic patient with orthopnea, this may require prior sedation and endotracheal intubation. If intubation is not an option and noninvasive ventilation is ineffective in relieving orthopnea, the femoral or brachial approach should be considered.

Difficult Insertion and Placement

Problems that occur during placement are generally of two types: (1) difficulty entering the central veins of the thorax and (2) difficulty directing the catheter tip into the PA. Both types of problem can be mastered only by gaining sufficient direct experience. With regard to central vein entry, placement of the introducer/sheath assembly is the crucial step. The internal jugular vein lies superficial and lateral to the carotid artery. Ultrasonic imaging with a purpose-designed instrument is a valuable aid in locating the vein, monitoring the puncture, and avoiding complications. Ultrasound can also be used to quickly scan the lungs after puncture attempts to assure the absence of pneumothorax. The stab incision made to facilitate the puncture must be sufficient to allow relatively easy passage of the vein dilator. Although catheter insertion must be gentle and never forced, dilator insertion may require traction of loose skin and subcutaneous tissues, especially in obese
individuals. The catheter may not always advance, especially when the reason for an apparently plump vein in the neck is blockage inside the chest.

Apart from anatomic aberrations (e.g., chronic vascular occlusion or downstream clotting), common reasons for difficulty encountered in floating a PA catheter tip to proper position include low CO, severe pulmonary hypertension with right ventricular (RV) overload and tricuspid regurgitation, and massive RV enlargement. The balloon should always be inflated cautiously and must fill easily without the need for force. If blood does not draw easily through the sheath assembly, concern is raised for extravascular placement. No catheter or sheath placed via the right internal jugular should cross the midsternal line on a well-centered routine pulmonary arterial chest film. A tip below the carina suggests right atrial placement. Although pulsatile blood flow raises the possibility of inadvertent arterial cannulation, it should be kept in mind that the jugular vein lies in close proximity to the innominate and carotid arteries. Therefore, patients with well-filled central veins as well as those with tricuspid regurgitation may exhibit impressively pulsatile blood flow from a well-placed CVP catheter. In questionable cases, transducing the catheter pressure is advisable. Although needle puncture of the artery usually has little consequence, a catheter actually placed into the carotid requires surgical consultation before attempts at removal.

![Diagram](image)

**FIGURE 2-4. Normal progression of the vascular pressure waveform in passage through the right heart to the balloon-occluded (wedge) position.** As a general rule, characteristic tracing changes indicating transitions between compartments are best judged by following the diastolic pressure and require 20 cm or less of catheter advancement before the abrupt step change is noted.

When the catheter is properly inserted via the right internal jugular vein, the balloon is inflated approximately 15 cm from the point of neck entry. Patients vary with regard to the dimensions of their vascular anatomy, but as a rule of thumb, the catheter tip should not require advancement by more than 20 cm beyond its current position before encountering the next vascular compartment (Fig. 2-4). In other words, an SVC tracing should be evident within 20 cm of skin entry, and the RV should be entered within 40 cm. The PA should be encountered within the first 60 cm of tip advancement (often considerably less). Coiling within the RV and misdirection of the catheter should be suspected after 45 to 50 cm has been advanced without securing an appropriate PA waveform. To facilitate placement, the patient can be repositioned (e.g., lateral...
decubitus or Fowler's) in an attempt to establish favorable balloon orientation and blood streaming for balloon flotation. Bedside ultrasound or fluoroscopy in the imaging department can be helpful in difficult cases. The latter is especially worthwhile to consider before attempting an insertion of a PA catheter from a femoral site, which tends to present more placement problems than brachial, subclavian, or jugular approaches.

**Interpreting Data from the Pulmonary Artery Catheter**

The balloon flotation catheter allows acquisition of three types of primary data: (1) central venous, PA, and balloon-occluded (wedge) pressures; (2) intermittent or continuous CO determinations; and (3) sampling of mixed venous or postalveolar capillary blood. This information can be used in its primary form or can be manipulated to provide useful indices of fluid volume status, right and left ventricular (LV) performance and loading conditions, or tissue perfusion (Table 2-1). Fiberoptic CVP catheters provide O₂ saturation data from the SVC in addition to CVP.

In recent years, justifiable concern has been raised that PA catheters often impair rather than improve the outcome of critical illness. An influential retrospective analysis of a large database published in the mid-1990s suggested that patients of equivalent severity were more likely to die when a catheter was used than when it was not. The data did not substantiate the suspicion that the instrument itself produced lethal illness by sepsis, balloon rupture of a pulmonary vessel, or other specific mechanism. Apprehension regarding its use was reinforced, however, by studies conducted in North America and Europe that revealed how inexpertly the data from the catheter were interpreted by critical care specialists. Although a general consensus has since emerged that PA catheters may provide important, therapy-guiding information, there is also agreement that the potential for iatrogenic injury is considerable and that numerous concepts of cardiopulmonary physiology must be mastered to interpret its data effectively. An important NIH ARDSnet trial of fluids and catheter strategies demonstrated neither survival benefit nor harm with use of the PA catheter. Widespread deployment of less invasive methodologies has sharply curtailed (but not eliminated) the need for its insertion in challenging patients.

<table>
<thead>
<tr>
<th>Table 2-1. Hemodynamic Data Provided by the PA Catheter&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td><strong>Direct</strong></td>
</tr>
<tr>
<td>Cardiac output</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Vascular pressures</td>
</tr>
<tr>
<td>Right atrium</td>
</tr>
<tr>
<td>Right ventricle</td>
</tr>
<tr>
<td>Pulmonary artery</td>
</tr>
<tr>
<td>Balloon occlusion (wedge)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Partial listing.
Pulmonary Vascular Pressures

Measurement of Pulmonary Vascular Pressures

Used in conjunction with the CO, the PA and wedge pressures yield important diagnostic information regarding intravascular filling, the tendency for pulmonary edema formation, the status of the pulmonary vasculature, and the vigor of LV contraction. Although less-invasive methods are now more commonly employed, PA catheterization often provides data of great value in assessing the relative function of the ventricles and the hydrostatic contribution of left heart failure and central vascular pressures to lung edema.

System Requirements for Accurate Pressure Measurement

STATIC REQUIREMENTS

Zeroing

Accurate recording of intravascular pressure requires error-free measurement of static pressure and faithful tracking of an undulating (dynamic) waveform. Attention must be paid to the technical details of data acquisition to avoid error. For wedge pressure recording, for example, an uninterrupted fluid column must extend from the left atrium (LA) through the catheter lumen to the flexible diaphragm of an electromechanical transducer. The transducer membrane deforms in response to pressure exerted by the fluid column and generates proportional electrical signals for amplification and display. Because this segment of the system is fluid filled, the vertical distance separating the LA from the transducer exerts a hydrostatic pressure against the sensor that adds to or subtracts from the actual (LA) pressure (Fig. 2-5). To eliminate bias from positioning, the transducer is placed at the LA level.

The display is then adjusted to read zero pressure when the dome is closed to the patient and opened to the atmosphere. Neither the transducer level relative to the LA nor the zero offset adjustment can be changed without a new “rezeroing” procedure. A similar caution to assure accuracy of positioning and zeroing applies to systemic arterial pressure monitoring. Sudden changes of systemic pressures are sometimes explained by movement of the transducer in relation to its originally zeroed position.
FIGURE 2-5. Zeroing the transducer. The transducer must not be moved from its original position after the display has been adjusted to record zero pressure with the liquid-filled system exposed to atmospheric pressure at the LA level. After zeroing, a hydrostatic column influences the recorded value when the transducer is lifted or lowered from its original position (left). Conversely, when the transducer remains at the “zeroed” position (right), movement of the catheter tip makes no difference to the pressure recorded, provided that a continuous column of fluid extends from the LA through the catheter to the transducer dome.

Calibration

Once the transducer is balanced (zeroed) to the LA level, the system must be accurately calibrated. With most modern systems, this step is accomplished automatically by the electronic processing equipment itself. As a final check that the zeroed and calibrated system is ready to record, the operator should shake the catheter tip through a substantial vertical range and observe the amplitude of the sinusoidal response on the monitor.

DYNAMIC REQUIREMENTS

Whatever the components and linkages, a well-calibrated system measures the mean vascular pressures rather accurately, unless the catheter itself becomes kinked or occluded. However, to track dynamic pressures faithfully, the liquid-filled portions of the system must have appropriate frequency-response characteristics. These properties are the natural resonant frequency of the system and its degree of damping. Without an appropriate frequency response, the system may exaggerate or attenuate important subcomponents of complex pressure waveforms. An improperly tuned system often generates erroneous systolic and diastolic pressure values and may not allow differentiation between distorted PA and wedge pressure tracings. Damping is produced by air bubbles, defective stopcocks, clot or protein debris within the catheter, impingement of the catheter tip against a vessel wall, and long, narrow, or kinked catheter tubing. After insertion, a simple check for adequate frequency response can be conducted using the rapid flush option of the catheter system (“snap test”) (Fig. 2-6). During the rapid flush, a sustained pulse of high pressure is temporarily applied to the transducer.
membrane. When the flush is suddenly terminated, pressure abruptly falls. Immediately upon sudden release, the tracing from a responsive system should overshoot (plunge below) its normal baseline and briefly (<1 second) oscillate before recovering a crisp, well-defined PA waveform. A poorly tuned system fails to overshoot or oscillate and recovers to a damped configuration after a noticeable delay.

FIGURE 2-6. The rapid flush (snap) test for determining the dynamic response of a catheter transducer system.

Accurately calibrated strip chart or frozen screen records of pulmonary vascular pressure should be referenced consistently to the same point in the respiratory cycle. For the wedge pressure, this is preferably at end expiration. Influenced by fluctuations of intrathoracic pressure, electronically processed digital displays of “systolic, diastolic, and mean” pressures may be misleading, particularly during forceful or chaotic breathing. The simultaneous recording of pulmonary wedge pressure ($P_w$), together with airway or (preferably) esophageal pressure facilitates interpretation.

Types of Pressure Measurement

CENTRAL VENOUS PRESSURE

CVP catheters serve a wide variety of clinical purposes. These lines primarily serve as secure and predictable routes for infusing drugs, nutrients, and volume expanders; the “triple-lumen” central catheters are invaluable for this purpose. Yet, although imperfect as an indicator of volume status or RV preload, the CVP tracing should not be ignored for the useful hemodynamic data it also provides. In the supine position, the mean CVP is virtually identical to the mean RA pressure. Used in conjunction with a volume challenge, mean CVP serves to index the adequacy of RV preload. A comparison of the central venous and wedge pressures proves helpful in diagnosing RV infarction and cor pulmonale. Furthermore, the contour of the CVP tracing can indicate tricuspid regurgitation caused by RV overload, suggest pericardial restriction and tamponade, or detect the cannon waves of AV block. The sawtooth pressure waves characteristic of atrial flutter can sometimes be detected on the CVP tracing when the surface electrocardiogram is inconclusive. In the absence of lung or heart disease, CVP serves well to indicate the degree of circulatory filling (e.g., during acute GI hemorrhage). Sudden and disproportionate elevations of CVP with respect to wedge pressure accompany pulmonary embolism with clot or air, RV infarction,
or acute lung disorders (bronchospasm, aspiration, pneumothorax). CVP is the downstream pressure component of the systemic vascular resistance (SVR) calculation. Superior vena caval $O_2$ saturation, which correlates well with (but slightly exceeds) the mixed venous value, may be very helpful in monitoring the efficacy of resuscitation from hypotension and shock. Modified fiberoptic CVP catheters can provide this information continuously.

Interpreted in conjunction with the wedge pressure, CVP can be used to estimate fluctuations in transmural filling pressure. Because the SVC is a flaccid structure embedded in the pleural space, fluctuations in CVP crudely reflect changes in intrapleural and pericardial pressures. It has been suggested that the CVP tracks changes in pleural pressure well enough that the transmission fraction of alveolar pressure to the pleural space can be computed under passive inflation conditions as follows:

$$\text{Transmission fraction} = \frac{(CVP_{EI} - CVP_{EE})}{(P_{PLAT} - P_{EX})}$$

where CVP$_{EI}$ and CVP$_{EE}$ are the end-inspiratory and end-expiratory values of CVP, and $P_{PLAT}$ and $P_{EX}$ are the corresponding static airway pressures recorded during occluded airway (stopped flow) maneuvers.

**PULMONARY ARTERY PRESSURE**

The RV generates the systolic PA pressure ($P_{PA}$) in forcing the CO through the pulmonary vascular network against resistance. Because the difference between mean arterial and venous pressures drives the flow, $P_{PA}$ can be made to rise by increasing the downstream venous pressure (as in LV failure), the CO, or the flow resistance (as in primary lung diseases). With its large capillary reserve, the normal pulmonary vascular bed offers little resistance to runoff. Consequently, at normal heart rates, pulmonary artery diastolic pressure ($P_{PAD}$) seldom exceeds LA pressure by more than a few mm Hg, even when flow is increased. Obliteration of pulmonary vascular channels, however, increases resistance, obligating a larger gradient of pressure. Under these conditions, $P_{PAD}$ may substantially exceed the pressure within pulmonary veins and LA. Just as importantly, the lack of recruitable vasculature reduces the compliance reserve that normally buffers $P_{PA}$ against fluctuations in CO. Consequently, significant variations in $P_{PA}$ often attend changes in output or vascular tone, making $P_{PAD}$ an unreliable index of LV filling in serious lung disorders. The pulmonary vascular network is designed to accept large (5- to 10-fold) variations in CO without building sufficient pressure across the delicate endothelial membrane to cause interstitial fluid accumulation and alveolar flooding. Therefore, the RV normally develops only enough power to pump against modest impedance. As a rule, the normal RV cannot sustain acute after loading to mean pressures greater than 35 mm Hg without decompensating. Over long periods, however, as during a protracted course of acute respiratory distress syndrome (ARDS), the RV strengthens and $P_{PA}$ builds. Indeed, the height to which $P_{PA}$ is forced to rise may be a useful prognostic index, correlating inversely with outcome. Given adequate time to adapt to massively increased afterload, systemic levels of arterial pressure can be sustained. Once the pulmonary vascular reserve is exhausted, an additional obliteration or narrowing by embolism, hypoxia, acidosis, or infusion of vasoactive drugs may evoke a marked pulmonary pressor response. Such elevations of hydrostatic pressure may cause fluid leakage, even across precapillary and postcapillary vessels.

**PULMONARY ARTERIAL OCCLUSION (WEDGE) PRESSURE**

Balloon inflation encourages the catheter tip to migrate from a main PA into a smaller caliber vessel, where it impacts and wedges. With the distal catheter orifice isolated from $P_{PA}$, fluid motion stops along the microvascular channels served by the occluded artery (Fig. 2-7). Because no resistive pressure drop occurs along this newly created static column, the pressure at the catheter tip equilibrates with the pressure at the downstream junction
It is believed that this junction normally occurs in a vessel of a size similar to that of the occluded artery—that is, in a large vein. Pulmonary wedge pressure, therefore, provides a low-range estimate of the mean hydrostatic pressure within the more proximal fluid-exchanging vessels. When resistance in the small veins is high, $P_w$ may not accurately reflect the true tendency for edema formation. Pulmonary capillary pressure is seriously underestimated when mean $P_{PA}$ substantially exceeds $P_w$. As a crude approximation, the pressure relevant to fluid filtration across the pulmonary vessels generally exceeds $P_w$ by about 40% of the difference between the mean PA and wedge pressures (Fig. 2-8).

**FIGURE 2-7. Definition of a wedge pressure ($P_w$).** The $P_w$, measured at point A, is nearly identical to the pressure at the junction of static and flowing venous blood (*). $P_w$ will not be influenced by partial occlusions of the static column (B) that extends from the catheter tip to the junction. However, obstructions (C) downstream from the junction point dissipate pressure, causing $P_w$ to significantly exceed mean $P_{LA}$. Although generally located in a large pulmonary vein, the junction point may reside in a small pulmonary venule in certain disease states.

Because large pulmonary veins are inherently low-resistance vessels, $P_w$ usually deviates little from $P_{LA}$. Mean $P_{LA}$, in turn, closely approximates left ventricular end-diastolic pressure ($P_{LVED}$) in the absence of mitral valvular
obstruction or incompetence or markedly reduced ventricular compliance. Because $P_{\text{LVED}}$ is the intravascular pressure component that determines preload, $P_w$ not only provides a low-range estimate of the hydrostatic pressure in the pulmonary venous circuit but also gives some indication of presystolic LV fiber stretch, especially when interpreted in conjunction with an estimate of extramural pleural pressure (e.g., by esophageal balloon).

![Damped PA Pressure vs. True Wedge Pressure](image)

**FIGURE 2-8.** Distinguishing a damped PA pressure ($P_{PA}$) tracing from a true wedge pressure ($P_w$) during balloon inflation. The mean pressure of a damped $P_{PA}$ tracing should approximate that of the undamped $P_{PA}$ waveform recorded with the balloon deflated (left). A true wedge pressure is distinguished by a mean pressure that is substantially lower than that of the $P_{PA}$ (right).

**OBTAINING A VALID WEDGE PRESSURE**

Unfortunately, a number of technical and physiologic factors encourage errors of data acquisition as well as misinterpretation of recorded values (Table 2-2). The validity of $P_w$ as a measure of pulmonary venous pressure depends on the existence of open vascular channels connecting the LA with the transducer. However, microvessels exposed to interstitial and alveolar pressures separate the catheter tip from the downstream “j” point. Because these vessels are collapsible, the interrelation between alveolar gas and fluid pressures governs the patency of the vascular pathway.

<table>
<thead>
<tr>
<th>Table 2-2. Checklist for Verifying the Position of PA Catheter</th>
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<tbody>
<tr>
<td>Desired Location (Zone III)</td>
</tr>
<tr>
<td>Respiratory variation of $P_w$</td>
</tr>
<tr>
<td>$P_w$ contour</td>
</tr>
<tr>
<td>Catheter tip location</td>
</tr>
<tr>
<td>PEEP trial</td>
</tr>
<tr>
<td>$P_{PAD}$ vs. $P_w$</td>
</tr>
</tbody>
</table>
Zoning

Conceptually, the upright lung can be divided into three zones, viewing the pulmonary vascular network as vulnerable to external compression by alveolar pressure (Fig. 2-9). These zones theoretically extend vertically because regional vascular pressures within the lung are affected by gravity, unlike the uniform gas pressure within the alveoli. In zone I, near the apex of the upright lung, alveolar pressure exceeds both $P_{PA}$ and pulmonary venous pressure, flattens alveolar capillaries, and essentially stops flow. In zone II, alveolar pressure is intermediate between $P_{PA}$ and pulmonary venous pressure, so that flow in this region is determined by the arterial-alveolar pressure gradient. In zone III, closer to the lung base, alveolar pressure is less than either vein or artery pressure and does not influence the flow. Inflation of the catheter balloon isolates downstream alveoli from $P_{PA}$. To sense pressure at the “j” point, the catheter tip must communicate with the pulmonary veins via a channel whose vascular pressure exceeds alveolar pressure. Intuitively, it would seem that only in zone III could patent vascular channels remain open to connect the catheter lumen and the LA. Outside zone III, alveolar pressure would exceed pulmonary venous pressure, collapsing the capillaries in those regions and forcing $P_w$ to track fluctuations in alveolar pressure, rather than $P_{LA}$. Although conceptually helpful, it is now clear that this simple schema does not always apply. “Zoning” seldom occurs so long as PEEP is less than 15 cm H$_2$O and the catheter tip lies at or below the level of the LA—its usual position. Furthermore, densely infiltrated or flooded alveoli may protect the patency of vascular channels, despite an unfavorable relationship between pulmonary venous pressure and the pressure within gas-filled alveoli. Shunted blood is not exposed to aerated alveoli.
Ascending vertically in the lung, arterial ($P_{PA}$) and pulmonary venous ($P_{PV}$) pressures decline relative to alveolar pressure ($P_{A}$), which remains uniform throughout the lung. In both zones I and II, $P_{A}$ exceeds $P_{PV}$ during balloon occlusion, collapsing alveolar vessels. Wedge pressure provides a valid measure of pulmonary venous pressure only when a continuous fluid column connects the catheter tip with the left atrium (e.g., zone III).

During spontaneous breathing in the supine position, the great majority of lung vessels normally remain in zone III throughout the respiratory cycle. The extent of zones I and II will increase when alveolar pressure rises relative to pulmonary venous pressure, as during hypovolemia, high PEEP, or during the inspiratory portion of a positive pressure breath. A catheter wedged outside zone III will show marked respiratory variation and an unnaturally smooth wedged waveform. In the absence of overt RV overload and failure, the respiratory fluctuation in $P_{w}$—influenced by alveolar pressure—will substantially exceed that of the CVP.

**Overwedging**

Even when the catheter tip is well positioned, asymmetrical balloon inflation or transverse orientation of the catheter axis relative to that of the vessel lumen can artificually elevate $P_{w}$ (overwedging) by isolating the catheter tip from the vascular lumen. Often, the catheter is too peripheral. When this occurs, the blind pocket of fluid bounded by the balloon and vascular wall continues to receive inflow from the continuous flushing system, forcing an elevation of the recorded pressure baseline. Under these circumstances, the balloon should be
deflated and the catheter gently flushed and repositioned, if necessary.

**Wedge Pressure as a Measure of Hydrostatic Filtration Pressure**

The pressure within the large pulmonary veins, the presumed “j” point, has long been regarded as a good reflection of the mean pressure within the fluid filtering vessels. It was once believed that the small capillaries were the only vessels to conduct significant fluid exchange with the interstitium and that very little pressure drop occurred beyond the capillary level. However, both assumptions now appear doubtful; extra-alveolar vessels clearly participate actively in fluid exchange. Furthermore, as much as 40% of the pulmonary vascular resistance (PVR) can be attributed to the capillaries and small veins. It is therefore likely that \( P_w \) may seriously underestimates the mean filtration pressure. Especially when the endothelium is leaky. Such discrepancies may help to account for hydrostatic edema occurring in the face of normal wedge pressure.

When \( P_w \) is used to estimate the hydrostatic contribution to edema formation, five additional factors should be considered: chronicity of the pathologic process, extravascular pressure, mean PA pressure, plasma oncotic pressure, and endothelial permeability (Table 2-3; Fig. 2-10).

An important role for plasma oncotic pressure is predicted by the classical Starling equation that describes transvascular fluid exchange (see Chapter 1). Capillary oncotic pressure is reduced by the hypoproteinemia of cirrhosis, malnutrition, nephrosis, or the administration of excessive crystalloid. Although clearly contributory in many settings, reduced plasma oncotic pressure alone rarely explains edema in the face of normal hydrostatic pressures and an intact capillary membrane.

<table>
<thead>
<tr>
<th>Table 2-3. Factors Relating Wedge Pressure to Pulmonary Edema</th>
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<tbody>
<tr>
<td>Magnitude of ( P_w )</td>
</tr>
<tr>
<td>Chronicity of the pathologic process</td>
</tr>
<tr>
<td>Diameter of wedged vessel</td>
</tr>
<tr>
<td>Plasma oncotic pressure</td>
</tr>
<tr>
<td>Pulmonary vascular permeability</td>
</tr>
<tr>
<td>Mean ( P_{PA} - P_w ) pressure difference</td>
</tr>
<tr>
<td>Cardiac output</td>
</tr>
<tr>
<td>Pulmonary vascular resistance</td>
</tr>
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</table>

Arteriolar

Venular
Normally, the curve relating lung water to PA occlusion pressure ($P_w$) demonstrates a sharp upward inflection as $P_w$ exceeds 20 to 25 mm Hg. Leakage is enhanced by high vascular permeability (e.g., ARDS), low serum osmotic pressure, and low extravascular pressure (as during forceful inspiratory effort). Conversely, a high $P_w$ may be well tolerated without excessive lung water accumulation if pleural pressure is increased or if pulmonary venous pressure is chronically elevated.

As already noted, endothelial permeability is a major factor governing the influence of $P_w$ on lung water accumulation. Unlike the curve relating $P_w$ to edema formation when permeability is normal, the steep relationship between these variables exhibits no distinct inflection pressure when permeability is increased. Thus, there does not appear to be a “safe range” of rising $P_w$ values over which accelerated edema formation can be completely avoided; when the lung is injured, even small changes in $P_w$ greatly influence the tendency for alveolar flooding.

**Wedge Pressure as a Measure of Left Ventricular Preload**

The diastolic ventricular volume that determines fiber length and preload is a joint function of myocardial distensibility (compliance) and the net transmural ("inside" minus "outside") pressure stretching the ventricle. Just as extravascular pressure must be considered when judging the hydrostatic tendency for fluid filtration, transmural pressure is the effective force distending the heart. As a close estimate of mean $P_{LA}$, $P_w$ is used clinically to judge the intracavitary filling pressure of the LV and thereby to monitor preload.

The other pressure determinant of precontractile fiber stretch, pleural pressure ($P_{pl}$), varies continuously throughout the respiratory cycle. Pulmonary wedge pressure must be interpreted cautiously, with attention directed toward the fluctuations in $P_{p1}$, which influence its transmural value. Although $P_{p1}$ is seldom measured directly, changes in $P_{p1}$ can be measured noninvasively with an esophageal balloon catheter. When the signal quality of the esophageal pressure ($P_{es}$) has been validated (e.g., by recording equivalent pressure deflections
during spontaneous efforts against a transiently occluded airway), referencing $P_w$ to esophageal pressure provides an acceptable monitor of changes in LV transmural pressure under most conditions, independent of $P_{pl}$ fluctuation. The fiber length achieved by any specific transmural pressure depends on ventricular compliance. Unfortunately, ventricular compliance is rarely known with precision and can change abruptly. The LV and RV are made interdependent by sharing muscle fibers, the septum, and the pericardial sac. Thus, the LV can stiffen when the RV distends in response to changes in PVR or volume loading. Ischemia, inotropic drugs, and circulating catecholamines can also produce abrupt but reversible reductions in diastolic compliance. Bedside ultrasound provides invaluable if less quantitative evidence regarding cardiac dimensions and “squeeze.” A balloon flotation PA catheter is available to track RV volume and ejection fraction by thermodilution. Reliable double indicator dilution (thermodilution/dye) systems for tracking central blood volume and lung water have also been developed that appear capable of rendering information of potential clinical and research value. The impact of both innovations on everyday medical practice, however, remains relatively modest.

**COMPENSATING FOR ELEVATED PLEURAL PRESSURE**

**Positive End-Expiratory Pressure**

Regardless of the mode of chest inflation, end exhalation often provides a convenient reference point for $P_w$ interpretation because during quiet breathing, $P_{pl}$ normally returns to its resting baseline at that time. End-expiratory $P_{pl}$ can exceed its normal value when the expiratory musculature actively contracts, tension pneumothorax is present, or elevated airway pressure at end exhalation increases lung volume (PEEP, auto-PEEP). If PEEP is intentionally applied and exhalation is passive, the relationship between the compliances of the lung ($C_l$) and chest wall ($C_{cw}$) determines the resulting elevation in pleural pressure:

$$\Delta P_{pl} = \Delta PEEP \times \left[ C_l / (C_l + C_{cw}) \right].$$

In the patient with normal lungs and chest wall, end-expiratory $P_{p1}$ increases by approximately one half of the applied PEEP during passive inflation because $C_l$ and $C_{cw}$ are similar over the tidal volume range. However, under conditions of reduced lung compliance and normal chest wall compliance (e.g., many cases of ARDS), the “transmitted” fraction may be very modest—one quarter of the PEEP value or even less. Thus, if a PEEP of 14 cm H$_2$O (10 mm Hg) is applied to the airways of a patient with ARDS, both $P_{p1}$ and $P_w$ at end exhalation should increase by approximately 2.5 mm Hg. These simple rules of thumb cannot be applied during active expiratory efforts.
FIGURE 2-11. The auto-PEEP effect and its measurement. In the presence of severe airflow obstruction and high ventilation requirements, alveolar pressure at end exhalation remains elevated as flow continues throughout expiration, driven by the recoil pressure of the hyperexpanded lung (left). Transiently stopping flow at end exhalation equalizes pressure throughout the lung and ventilator circuit (right). Occult alveolar pressure is then detectable by the ventilator.

**Auto-PEEP (Intrinsic PEEP)**

When insufficient time is allowed between the ventilatory cycles for the chest to deflate to its relaxed volume, airflow continues across critically narrowed airways throughout exhalation, driven by an alveolar pressure higher than airway opening pressure. This results in an occult “auto-PEEP” (intrinsic PEEP) effect at the alveolar level. Auto-PEEP is most likely to occur in patients with airflow obstruction who require high minute volumes, but because the endotracheal tube and exhalation valve are highly resistive elements, it can also develop at any time minute ventilation is significantly elevated—even in normal subjects. Inverse ratio ventilation, airway pressure release ventilation (APRV), and high-frequency ventilation are other settings in which high levels of auto-PEEP can be encountered. Compliant lungs and stiff chest walls (e.g., obesity, burns, abdominal surgery, ascites) transmit a high percentage of alveolar pressure to the pleural space, producing large fractional increases in $P_{p1}$ and $P_w$. In the setting of severe airflow obstruction, this is often half or more of the auto-PEEP value. Unless accounted for, auto-PEEP effects may encourage overestimation of intravascular volume and prompt inappropriate therapy. Although unmeasured during normal ventilator operation, the auto-PEEP level is detectable by the simple bedside maneuver of expiratory port occlusion at the end of passive exhalation (Fig. 2-11).

**Active Exhalation**

Active exhalation and chaotic breathing present other difficult problems in the interpretation of the wedge pressure. In theory, the effect of vigorous breathing can be overcome by simultaneously recording $P_{es}$ or by giving short-acting muscle relaxants during the measurement. Silencing respiratory efforts, however, dramatically alters hemodynamic status and may mask any diastolic dysfunction that occurs under the stress (and increased LV afterload) of vigorous breathing. It does, however, give some indication of whether diuresis is indicated. A high $P_w$ under passive conditions suggests the potential for hydrostatic edema during active breathing. Even when transmural $P_w$ can be computed with certainty, effective preload is difficult to estimate without the knowledge of the myocardial pressure-volume relationship.

**Principle of Functional Monitoring**

It is always hazardous to infer the status of a dynamic system from a single number. The monitored “challenge” is a key maneuver in determining hemodynamic reserves and should be conducted using information from as many monitoring methods as are readily available—physical examination, vital signs, ultrasonography, and directly monitored intravascular pressures and flows. Challenging may involve reversible noninvasive maneuvers (e.g., PEEP, measurement of PPV of BP with the respiratory cycle, or leg lifting), rapid fluid bolusing or diuresis, and/or inotrope administration.

**The Fluid Challenge**

Except when the calculated transmural $P_w$ is very high or very low, decisions regarding fluid therapy of a patient in an oxygenation or perfusion crisis are often best made by an empirical trial of rapid volume loading (a fluid challenge). Systemic BP, CO, heart rate, central vascular pressures, and the physical examination are monitored before and after a rapid infusion of physiologic saline or colloid. A fluid bolus
(250 to 500 mL) is administered over 5 to 20 minutes, depending on the suspected cardiovascular fragility of the patient. If hemodynamic variables improve with little change in the measured CVP or \( P_w \), administration of additional volume is prudent. Conversely, marked increases of heart rate or of \( P_w \) (>5 mm Hg), together with marginal improvement in BP and CO, indicate that increasing the rate of volume infusion risks pulmonary edema with little hemodynamic benefit.

**FIGURE 2-12. Passive leg raising test.** The head must be lowered and the feet raised to elicit the desired preloading challenge. Preferably, the monitored variable is a flow-associated indicator and the patient remains similarly calm in both positions.

**The Leg Lift (Passive Leg Raising)**

Translocation of blood from the periphery to the central vascular compartment may be made quickly and reversibly using the gravitational forces of a leg lift. Raising the legs 45 degrees relative to the supine torso will reversibly translocate approximately 250 to 400 mL of blood to the central compartment (Fig. 2-12). The volume of blood relocated in this way varies with body size and vascular filling status. Ideally, CO or stroke volume are measured during a 1-minute lift, looking for at least a 10% improvement in these flow indices. In practice, cruder indicators such as MAP are often followed. As already noted, the value of the passive leg raising (PLR) is that it is reversible and can be applied to patients with arrhythmias and spontaneous efforts as well as those being passively inflated.

**Cardiac Output Determination**

**Measurement**

**FICK PRINCIPLE**

In its simplest form, the primary basis for CO determination, the Fick principle, can be explained as follows. The quantity of any marker contained within a static volume is the product of that volume and its concentration. In a dynamic system into which a marker is continuously added and lost, the introduction rate of the marker is the product of flow rate and its concentration difference across the region of loss. In the steady state, no net addition or loss of the marker occurs. For example, if arterial oxygen is being consumed by the body and replenished by the lungs at equal rates, the \( \dot{V} \) is the product of CO and the \( \Delta O_2 \) concentration difference between systemic arterial and mixed venous (PA) blood. Therefore, if the \( O_2 \) consumption rate is known or readily estimated, determining the \( O_2 \) contents in systemic and PA blood samples allows calculation of the flow rate (CO). Under non-steady-state conditions, however, these calculations can be wildly erroneous.
THERMODILUTION

A similar principle applies during determinations of CO by thermodilution, where the marker that is injected and dissipated is thermal deficit, or “cold,” and its rate of disappearance as it is diluted by the warm venous blood is an indication of blood flow. Although all PA catheters can provide a sample of mixed venous blood for use in an oxygen-Fick determination, thermodilution capability allows more convenient, repeatable, and precise measurement of forward blood flow. A sensitive, rapidly responding thermistor bonded to the catheter tip continuously senses temperature, altering its electrical resistance in response to thermal changes within PA blood. As a side benefit, the thermistor provides a highly reliable, continuous readout of core body temperature. When a bolus of cooler, room temperature fluid enters the right atrium (RA), it mixes with warm venous blood returning from the periphery. The churning action of the RV homogenizes the two fluids, and the thermistor records the dynamic thermal curve generated when the mixture washes past the proximal PA. The relationship linking output to temperature is the Stewart-Hamilton formula:

\[ \dot{Q} = V(T_B - T_I)K_1K_2 / \int T_B(t)dt \]

where \([Q with dot above] = CO; V = \text{injected volume}, T_B = \text{blood temperature}, T_I = \text{injectate temperature}, T_B(t)dt = \text{change in blood temperature as a function of time, and} K_1 \text{ and } K_2 \text{ are computational constants. The components of the numerator are either known constants (} V, K_1, K_2 \text{) or measured values (} T_B, T_I \text{). The denominator is the area beneath the time-temperature curve, derived by computer integration of the thermistor signal. When close attention is paid to the method of data acquisition, thermodilution CO values compare favorably with those obtained by the steady-state O_2 Fick method and by dye dilution.}

Technical Considerations and Potential Errors

Thermistor Position

Except for a few rather obvious exceptions, most technical errors in CO determination result in over-estimation of the true value. To generate a valid estimate of output, the thermistor should sample a well-mixed cold charge of known strength and must lie freely within the lumen of the central PA. Impaction against a vessel wall or encapsulation by clot tends to insulate the thermistor from the cool stream, falsely elevating the reported value. A P_PA waveform that appears damped or wedged may indicate malpositioning and potential problems. It is a good clinical practice to inspect the temperature-time profile periodically, especially when the value conflicts with the rest of the clinical picture, extreme variability is encountered among serial estimates, or another question of temperature accuracy exists. A valid curve shows a rapid early descent to a trough value, smoothly returning to baseline within 10 to 15 seconds of injection.

Tricuspid Regurgitation

The computer integrates the volume under the temperature-time curve assuming unidirectional flow, no loss of signal amplitude, and no delay in signal detection. Tricuspid regurgitation, which occurs very commonly in acute cardiopulmonary disorders, can violate one or more of these assumptions, leading either to overestimation or underestimation of the true value. Such artifacts should be suspected when the value seems discordant with the remainder of the database or when there is a sudden and otherwise unexplained change in measured output. Validity may also be compromised by intracardiac shunting, thermistor shielding by wall contact or clot, and inadvertent augmentation of the cold charge by concomitant rapid administration of intravenous fluids near the RA.

EJECTION FRACTION, VENTRICULAR VOLUME, AND “CONTINUOUS” CARDIAC OUTPUT DETERMINATIONS

Historically, the episodic injection of cool liquid has been used to implement thermodilution technique. When a
modified PA catheter is fitted with a rapid-response thermistor and electrodes for sensing and gating beat-to-beat changes in temperature, good estimates for RV ejection fraction (RVEF) can be made. With estimates for CO, stroke volume, and RVEF in hand, RV volume can then be calculated. The latter to be a more reliable indicator of preload status and fluid responsiveness than pressure-based measures, but this remains controversial. Another thermal-based approach is to repeatedly inject small slugs of heat at the RA/RV level using a resistance element. Blood temperature is monitored near the catheter tip a short distance downstream. This method serves as the basis for near-continuous measurement of CO, RV stroke volume, and chamber volume estimation. Data from these instruments appear to agree well with those from conventional thermodilution techniques and are now widely deployed in the clinical setting.

MINIMALLY INVASIVE NONTHERMAL METHODS FOR CARDIAC OUTPUT DETERMINATION

Although thermodilution remains well entrenched as the standard for CO estimation, it needs often arise for gathering such data without invasive catheterization. Several interesting methods that do not require central vascular access have been introduced into practice: noninvasive expired carbon dioxide analysis, lithium dilution, esophageal Doppler, pulse contour analysis, and thoracic electrical bioimpedance all have physiologic rationales and limitations for applications in intensive care (Table 2-4). The expired CO\textsubscript{2} method tracks the rate of CO\textsubscript{2} excretion during partial rebreathing, which is proportional to the pulmonary blood flow and the product of the arteriovenous difference in CO\textsubscript{2} content. Estimates for \[\dot{V}O_2\] and for arterial CO\textsubscript{2} content can be made from the exhaled gas profile, and rebreathing eliminates the need for mixed venous CO\textsubscript{2} content measurement. At the present time, this method requires an intubated patient under approximately steady-state metabolic conditions. Its accuracy is questionable when PCO\textsubscript{2} is not linearly related to content (PaCO\textsubscript{2} < 30 mm Hg) and in settings where seriously diseased lungs generate a large right-to-left shunt fraction.

<table>
<thead>
<tr>
<th>Table 2-4. Minimally Invasive Cardiac Output Determination</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Expired CO\textsubscript{2} (modified Fick) analysis</td>
</tr>
<tr>
<td>• Lithium dilution</td>
</tr>
<tr>
<td>• Esophageal Doppler</td>
</tr>
<tr>
<td>• Arterial pulse contour analysis</td>
</tr>
<tr>
<td>• Thoracic bioimpedance/reactance</td>
</tr>
</tbody>
</table>

CO by lithium dilution requires venous injection of lithium chloride and peripheral measurement of its concentration in a small sample of arterial blood. Such values appear to correlate well with traditional thermodilution estimates. Pulse contour analysis is based on the concept that the arterial pulse waveform is influenced by stroke volume, which can be estimated as the integral of the end-diastolic to end-systolic pressure divided by the aortic impedance. The latter requires validation of CO determined by another method (e.g., lithium dilution). Once calibrated, however, pulse contour analysis tracks CO changes with acceptable accuracy. Unfortunately, its sensitivity is impaired in low flow and arrhythmic states.

Thoracic electrical bioimpedance, the least interventional of any of these methods, measures the resistance of the thorax to a high-frequency, very low-magnitude current applied using multiple thoracic electrodes. Because
Electrical impedance is inversely proportional to fluid content, changes in CO are reflected as changes in conductivity. This method is influenced by fluid content unrelated to CO and, therefore, is not sufficiently accurate for absolute CO determinations in the severely ill. (It fares better in tracking trends.) Finally, esophageal Doppler methodology requires placement of a Doppler probe in close proximity to the descending aorta, where it can assess aortic cross-sectional area and blood flow velocity. Multiple estimates and approximations are needed, and though it is likely to give good trending information, its accuracy for absolute CO determinations and its long-term reliability remain questionable for applications in critical care.

Conceptual Advantages and Limitations of Noninvasive Cardiac Output Measurements

CO is of high value in classifying patients with regard to cardiac compromise and in assessing responses to therapy. In mildly to moderately ill patients, noninvasive measurements are acceptably accurate and may serve each purpose admirably if they are combined with other information gathered from the physical examination, clinical laboratory, ultrasonography, and measurements of central venous oxygen saturation (see following). For certain purposes (e.g., qualitatively following the response to vasoactive agents or fluid loading), trending data may be helpful even when precision is compromised by serious illness or refusal of the patient to undergo invasive instrumentation. Yet, in most seriously ill patients, these methods do not substitute for a well-functioning PA catheter, which still offers the more complete and accurate set of data needed to acquire an integrated picture of the patient's hemodynamic status.

Clinical Interpretation of Cardiac Output

Important diagnostic information can often be obtained regarding the functional status of the heart and the vasculature by combining measures of CO and ventricular filling pressure. The fluid challenge is particularly helpful for this purpose. However, CO must be interpreted in relation to the mass and the metabolism of the patient. A CO of 3.5 L/min may suffice for the needs of a hypothermic, cachectic 50-kg patient, but the same CO may be associated with a circulatory crisis in a previously healthy 100-kg burn victim. The cardiac index (CI, CO/surface area) attempts to adjust for variations in tissue mass. Body surface area (BSA) can be determined from standard nomograms or can be approximated by this regression equation:

\[
BSA = 0.202 \times \text{wt}^{0.425} \times \text{ht}^{0.725}
\]

where BSA is expressed in square meters, weight (wt) in kilograms, and height (ht) in meters. Used alone, however, even the CI is of limited help in assessing perfusion adequacy. Over a broad range, any given value for CI may be associated with luxuriant, barely adequate, or suboptimal tissue \(O_2\) transport, depending on hemoglobin concentration, metabolic requirements, and blood flow distribution. Measures of urine output and metabolic acid production (anion gap, serum lactate) together with indices of tissue \(O_2\) utilization (e.g., \(O_2\) extraction) provide better guides of perfusion adequacy.

Indices of Vascular Resistance

The CO measurement can be used in conjunction with pulmonary and systemic pressure measurements to compute the vascular resistance values needed to gauge ventricular afterload and diagnose the etiology of a hypotensive crisis. These indices of vascular resistance complement the mean systemic BP in guiding vasodilator and vasopressor therapy. PVR and SVR are crude indices, calculated as if blood flow fulfilled the assumptions of Poiseuille law for laminar flow:

\[
PVR = (P_{PA} - P_w) / CO \quad \text{and} \quad SVR = (MAP - P_{RA}) / CO
\]
where \( CO \) = cardiac output, \( \text{MAP} \) = mean systemic arterial pressure, \( \text{Pa} \) = mean PA pressure, and \( \text{PRA} \) = mean right atrial pressure.

Although PVR and SVR are commonly used in the clinical setting, vascular resistance calculations should preferably be referenced to BSA, using the CI (instead of CO). The resulting values, the systemic (SVRI) and pulmonary (PVRI) indices, avoid the misleading variations of the raw parameters due to body size. Significant elevations of PVRI reliably indicate underlying lung pathology, reflecting the interplay of constrictive and occlusive forces on a compromised pulmonary capillary bed. Unfortunately, however, the complex relation between PVR and CO often confounds physiologic interpretation. Changes in the PVRI should be evaluated with full awareness that the PVRI is a function of blood flow. In fact, the magnitude of PVR, as well as its response to an intentional change in CO, may serve as a useful prognostic index in such acute lung diseases as ARDS. Failure of PVR to rise in response to a boost in CO suggests ample vascular reserve; conversely, a sharp increase in PVR that parallels CO indicates extensive obliteration of the pulmonary vascular bed. SVR may rise homeostatically to high values in support of suboptimal CO, helping to maintain an appropriate perfusion pressure across vital capillary beds. However, an excessive elevation of SVR can impair the performance of weakened LV. An error in CO measurement may seriously alter the computations of vascular resistance and thereby misdirect classification or management of the clinical problem.

**Oxygen Delivery**

CO data find one of their most useful applications in the management of hypoxemia. Because tissues attempt to extract the amount of oxygen required to maintain aerobic metabolism, the mixed venous \( O_2 \) tension falls when \( O_2 \) delivery (the product of CO and arterial \( O_2 \) content) becomes insufficient for tissue needs. If the fraction of venous blood shunted past the lung remains unchanged, arterial \( O_2 \) tension may fall impressively as abnormally desaturated blood blends with postcapillary blood from better ventilated lung units. Thus, depressed CO values may contribute to hypoxemia, and variations in

CO may sometimes explain the otherwise puzzling changes in arterial \( O_2 \) tension. As a primary determinant of \( O_2 \) delivery, CO measurements often prove helpful during selection of the appropriate PEEP level for the patient with life-threatening hypoxemia. Depression of venous return coincident with PEEP application may occasionally nullify any beneficial effect of improved pulmonary gas exchange on tissue \( O_2 \) delivery (see Chapter 9).

**Lactate, Anion Gap, and Central Venous Gases**

A rational goal of resuscitative therapy of severe sepsis and shock is to restore balance between oxygen delivery and demand by increasing CO. Evaluation of overall hemodynamic adequacy is aided greatly by serial determinations of serum lactate, anion gap, and central venous blood gases. Although both lactate and anion gap can be elevated by other pathologic conditions, lactate values that exceed 4 mmol/L in conjunction with low venous \( \text{SvO}_2 \) and elevated central venous \( \text{PCO}_2 \) (liberated by H+ ion buffering) strongly suggest the activation of anaerobic metabolic pathways. These deficits may respond to restoration of hemodynamic balance. Although elevated lactate and anion gap do not necessarily correlate with severity of hemodynamic compromise, a consistently falling lactate value strongly suggests its gradual resolution. Aggressive goal-oriented resuscitation to near-normal values of central venous oxygen saturation in the earliest phase of septic shock management (\( >70\% \)) appears to improve mortality risk. Once that target is achieved, the existing literature does not favor raising CO and central venous \( O_2 \) saturations further.

**Sampling of Central Venous and Mixed Venous Blood**
Oxygen Supply and Demand

Analysis of mixed venous blood provides valuable information in evaluating the oxygen supply-demand axis. Blood flow to individual organs (e.g., the kidneys) is not precisely governed by metabolic rate, so venous O$_2$ content varies widely among tissues. Normally, blood from the inferior vena cava (IVC) is more fully saturated than is blood from the SVC. During shock states, however, the converse is often true. Samples drawn from either of these central vessels or from the incompletely blended pool within the RA are not entirely representative of the true mixed venous value. Blood withdrawn from the proximal PA, however, has been merged in the RV and is therefore more appropriate for analysis. Care should be taken to withdraw blood slowly, with the balloon deflated and the catheter tip positioned in the proximal PA. Otherwise, contamination from the postcapillary region may artifactually increase the oxygen content.

Although it is generally acknowledged that the saturation of blood withdrawn from the SVC will differ somewhat from the mixed venous value, the differences are not usually great, and the need to access the PA has been questioned when following trends is the key concern, and early resuscitation with adequate fluid volumes is the top priority. Central venous cannulation can usually be accomplished quickly and is required for pressor administration. Using repeated (or continuously recorded) saturations from a CVP catheter may allow timely assessment of fluid resuscitation adequacy under emergent circumstances, as in severe sepsis and shock. Even though its value has been documented in the latter condition, it remains debatable whether this approach offers parallel benefit in other resuscitation settings.

The value of mixed venous blood analysis is best understood in the framework of tissue O$_2$ demand-supply dynamics. Briefly, the product of CO and arterial oxygen content defines the overall rate of O$_2$ delivery. Each organ receives a variable percentage of the total amount, a flow that may be luxuriant, just adequate, or insufficient to satisfy its aerobic metabolic demand. The O$_2$ tension (PvO$_2$) and saturation (SvO$_2$) of the venous effluent reflect the balance between supply and need. When flow does not rise to meet increased tissue demands, more O$_2$ is extracted from each milliliter of capillary blood, and PvO$_2$ and SvO$_2$ fall. Conversely, when the O$_2$ transport/demand ratio increases, the arteriovenous oxygen content difference narrows and PvO$_2$ and SvO$_2$ rise. PvO$_2$ and SvO$_2$ may not reflect serious perfusion deficits if arterial blood is anatomically or functionally shunted past metabolizing tissue. For example, in cirrhosis, cyanide poisoning, or the early phases of sepsis, nonnutritive flow may cause SvO$_2$ to be normal or high, despite serious tissue hypoxia. Because of these distribution and utilization pitfalls, it is always wise to compute the anion gap, monitor lactate, and determine PCO$_2$ simultaneously. Acutely developing depressions of venous O$_2$ tensions, when sustained, reliably signal increased tissue O$_2$ extraction caused by anemia or an impending perfusion crisis, especially when complemented by a central venous PCO$_2$ elevation.

Uses and Limits of Mixed Venous O$_2$ Saturation

The mixed venous oxygen saturation correlates inversely with physiologic stress in acute myocardial infarction, acute respiratory failure, and shock. As O$_2$ delivery is reduced from its usual level without a matching change in O$_2$ demand, tissues initially compensate by maintaining oxygen consumption ($\dot{V}$O$_2$) at the expense of a falling SvO$_2$ (Fig. 2-13) (quantified by the tissue oxygen extraction ratio: \([\text{SaO}_2 - \text{SvO}_2]/\text{SaO}_2\)). However, beyond a certain critical value of O$_2$ delivery, the O$_2$ extraction mechanism reaches the limits of compensation, SvO$_2$ stabilizes, and $\dot{V}$O$_2$ becomes delivery dependent. Once this critical value is
reached, SvO\textsubscript{2} becomes an insensitive monitor of changes in perfusion. Such delivery dependence has been demonstrated both in experimental animal models of acute lung injury and in certain clinical settings. Below this critical value of O\textsubscript{2} delivery, anaerobic metabolism must supplement aerobic mechanism. The SvO\textsubscript{2} at which this limit occurs varies, depending on whether the delivery was reduced by anemia, arterial hypoxemia, or falling CO. Despite the importance of PvO\textsubscript{2} as a global indicator of end-capillary tissue O\textsubscript{2} tension, PvO\textsubscript{2} can vary with alterations in the affinity of hemoglobin for O\textsubscript{2}, even when O\textsubscript{2} content remains stable. Therefore, direct assessment of SvO\textsubscript{2} is preferred for clinically evaluating the oxygen-perfusion axis; estimation of SvO\textsubscript{2} from PvO\textsubscript{2}, pH, and temperature is fraught with error because of the steepness of the O\textsubscript{2} tension-saturation relationship. Traditionally, SvO\textsubscript{2} has been determined on individual blood samples analyzed by laboratory instruments that measure SaO\textsubscript{2} by transmission oximetry (co-oximeter) or O\textsubscript{2} content by fuel cell determination. The application of fiberoptic reflectance oximetry to central venous and balloon flotation catheters has enabled continuous bedside monitoring of SvO\textsubscript{2}. Continuous measurement of SvO\textsubscript{2} also speeds the process of determining the optimal PEEP level because alterations in net tissue O\textsubscript{2} flux are made quickly apparent.

![Diagram of oxygen delivery vs. oxygen consumption and saturation of mixed venous blood](image)

**FIGURE 2-13.** Relationship of oxygen delivery to oxygen consumption ([\(\dot{V}\) with dot above]O\textsubscript{2}) and to the saturation of mixed venous blood (S[v with bar above]O\textsubscript{2}). As oxygen delivery is reduced from the normal value (e.g., by reducing CO), all the metabolic demands remain unchanged. Increased extraction can initially maintain oxygen consumption at the cost of a falling S[v with bar above]O\textsubscript{2}. At some critical level of oxygen delivery, the limits of extraction are reached, forcing [\(\dot{V}\) with dot above]O\textsubscript{2} to become delivery dependent.

Changes in SvO\textsubscript{2} have no unique interpretation and must be viewed in light of the variables that determine O\textsubscript{2} transport and demand—the amount and distribution of CO, hemoglobin concentration and function, arterial O\textsubscript{2}
tension, and metabolic rate. Although a change in SvO₂ does not indicate which of the multiple factors comprising the Fick equation is responsible, integration of SvO₂ with clinical observations, blood gas information, and CO data often establishes an early, if presumptive, diagnosis (Fig. 2-14). Declining values for SvO₂ and CO, together with unchanging PaO₂, imply hemodynamic deterioration, whereas a rising CO with a falling SvO₂ are consistent with increased metabolic demand or acute loss of circulating blood volume (e.g., hemorrhage). Experience with the fiberoptic catheter as an online monitor has underscored the rapidity with which SvO₂ responds to transient changes in metabolism or altered O₂ delivery. Sensitivity to such changes is undoubtedly enhanced when the heart is unable to raise its output sufficiently in response to stress. Then, SvO₂ must reflect altered arterial oxygenation or increased O₂ demand, undampened by the buffering effect of cardiac compensation. Such wide fluctuations may help explain why SaO₂ often varies markedly in the absence of convincing clinical improvement or deterioration.

### DETERMINANTS OF SVO₂

\[
\dot{V}_O₂ = \dot{Q} \left( C_aO₂ - C_vO₂ \right)
\]

\[
\dot{V}_O₂ \propto \dot{Q} \text{Hgb} (SaO₂ - S\tilde{V}O₂)
\]

\[
S\tilde{V}O₂ \propto \text{SaO₂} - \left( \frac{\dot{V}_O₂}{\dot{Q}\text{Hgb}} \right)
\]

\[
S\tilde{V}O₂ \propto \text{SaO₂} - \left( \frac{O₂ \text{Consumption}}{O₂ \text{Delivery}} \right)
\]

**FIGURE 2-14.** Key measurable determinants of the mixed venous oxygen consumption under steady-state conditions.

SvO₂ often falls in advance of detectable changes in the primary hemodynamic variables, and a downward trend may alert the clinician to intervene. A decline in SvO₂ may be the first indication of occult bleeding, incipient pump failure, or impending cardiac arrest. Conversely, an increasing SvO₂ may indicate improvement or signal the onset of sepsis. Rapid and convincing changes in SvO₂ accompany drug therapy (vasopressors, vasodilators, sedatives), intravascular volume manipulation (diuresis, fluid infusion, transfusion), position shifts, and ventilatory changes.

**Complications of the Pulmonary Artery Catheter**
Apart from any harm caused by errors in the acquisition or interpretation of data, the complications of PA catheterization arise during insertion, during manipulation of the catheter, and as a result of its residence within the central vascular structures (Table 2-5).

### Table 2-5. Common Complications Pulmonary Artery Catheter Insertion

<table>
<thead>
<tr>
<th>Complication</th>
<th>Cause</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>Catheter coiling or excess catheter in RV</td>
<td>ECG monitoring</td>
</tr>
<tr>
<td></td>
<td>Catheter tip reentry into RV from PA</td>
<td>Follow the “rule of 20s” Expedient catheter passage</td>
</tr>
<tr>
<td></td>
<td>Hypoxemia, coronary ischemia, electrolyte disturbances</td>
<td>Reverse hypoxemia, electrolyte disturbances</td>
</tr>
<tr>
<td>Complete heart block</td>
<td>Preexisting left bundle-branch block</td>
<td>Temporary pacer on standby</td>
</tr>
<tr>
<td>Catheter malpositioning</td>
<td>Forceful insertion</td>
<td>Advance only with caution</td>
</tr>
<tr>
<td>Extracardiac</td>
<td>Forceful insertion</td>
<td>Consider fluoroscopy</td>
</tr>
<tr>
<td>Catheter knotting</td>
<td>Excessive catheter length</td>
<td>Follow the “rule of 20s”</td>
</tr>
<tr>
<td></td>
<td>Extensive manipulation</td>
<td>Do not insert &gt;15 cm into the PA</td>
</tr>
<tr>
<td>Dilated heart</td>
<td></td>
<td>Consider fluoroscopy in difficult cases</td>
</tr>
</tbody>
</table>

### Insertion-Related Complications

#### Catheter-Related Arrhythmias

Premature atrial and ventricular contractions commonly occur during insertion of the Swan-Ganz catheter, especially when the patient is predisposed to them. Failure to inflate the balloon adequately, slow passage
of the catheter through the heart, and insertion of an excessive length of catheter are likely contributors. Special caution should be exercised if the patient is hypoxemic or has an electrolyte disturbance at the time of instrumentation. Complete heart block has been reported to follow the insertion of the PA catheter in patients with preexisting conductor system disease, as transient right bundle-branch block occurs commonly during this procedure. Although the risk is probably not as great as once feared, it is advisable to have a temporary pacemaker available prior to inserting the catheter in a patient with preexisting left bundle-branch block.

**Catheter Malpositioning**

Experience is the most important determinant of successful catheter placement. Although often difficult and time consuming, vascular access should never require forceful insertion. The clinician must be thoroughly familiar with the pressure tracings that arise from the various cardiovascular structures encountered and be aware of departures from the “rule of progressive 20s” (see Fig. 2-4).

**Pulmonary Infarction**

Pulmonary infarction is distressingly common. Persistent wedging of the catheter tip and the dislodgement of clot formed on the catheter are the most likely explanations. Infarction occurs rarely when the catheter is well positioned (tip within the main PA), and the balloon requires its maximum volume (1.25 to 1.5 mL) for inflation to the wedge position.

**Pulmonary Artery Rupture**

PA rupture can cause fatal hemoptysis. Several factors predispose PA perforation: advanced age, hypothermia, and pulmonary hypertension. Women are disproportionately represented. Overinflation of a catheter balloon in a small PA is the most likely mechanism. Therefore, the balloon should never be inflated abruptly, and inflation should be stopped immediately when there is evidence either of the approach to the wedge position or of overwedging. Advancing the catheter tip without balloon inflation should never be undertaken.

Although a variety of therapeutic measures have been suggested, such as the application of PEEP, deliberate balloon inflation, and positioning with the catheter with its tip side down, their efficacy is not proven. Maintenance of the airway and support of the circulation are the first priorities as for any patient with severe hemoptysis. It seems prudent not to deflate the balloon until definitive therapy is imminent.

**Complications Related to Long-Term Catheterization**

**Thrombosis**

Although thrombosis about the catheter at its insertion site or at various points along the catheter occurs very commonly, serious consequences are not commonly encountered. Yet, thrombosis at or near the insertion site may result in subclavian vein thrombosis, superior vena caval syndrome, or internal jugular vein occlusion. The indwelling catheter may also result in platelet consumption, pulmonary emboli, or right-sided valvular damage. These complications seldom rise to the level of clinical significance in most patients.

**Infection**

Any indwelling catheter may produce serious infection. To minimize contamination, a chlorhexidine sponge is placed at the site of skin contact during insertion. Inspection of the puncture site for signs of inflammation is facilitated by dressings with a clear transparent window. When oozing of bleeding is observed at the time of insertion, however, gauze dressings are preferred. Inspection of the entry site and change of dressings is
advisable on a daily basis. After strict attention is paid to sterile insertion technique, meticulous care of all catheter lines, stopcocks, transducers, and infusions must be taken; most catheters can be used for more than 72 hours without serious infectious complications. The incidence of infection tends to rise thereafter. If the local site looks uninflamed and the patient remains afebrile, a catheter can remain in place for 5 days or more without serious risk. Many practitioners, however, change PA catheters at approximately 96 hours, but there is no set standard in this regard.

Whenever the patient is febrile or septic, blood cultures should be obtained from the catheter and at least one peripheral site. The catheter removed expediently if it appears to be the most likely source. Assuming that the local site does not appear infected, some practitioners insert a fresh catheter without changing the site of insertion. This practice, however, is controversial. When a PA catheter is in place and the local site appear suspicious, the introducer must be removed along with the catheter and a fresh site selected—assuming that the catheter is still required.

**ECHOCARDIOGRAPHY, ULTRASOUND, AND OTHER IMAGING TECHNIQUES**

Neither standard ECHO nor radionuclide ventriculography provides continuous information and therefore cannot properly be considered a true monitoring technique. Yet, each has an important place in characterizing the nature of cardiac pathology in the intensive care unit (ICU). These methods allow the physician to answer specific diagnostic questions and to categorize the overall structure and performance of the heart as well as to estimate chamber dimensions. In a sense, they can be considered complementary to central venous, pulmonary, and systemic arterial monitoring.

**Echocardiography**

*General Principles*

ECHO provides a valuable bedside method for the noninvasive assessment of cardiac function. The ECHO probe both emits a high-frequency (1 to 10 MHz), rapidly pulsed ultrasonic signal and receives its acoustic reflection. These data are then integrated to form an interpretable image. Appropriate contrast agents often enhance the sonic differentiation of anatomic structure. Three different ECHO techniques have been introduced into clinical practice: (1) M-mode, which provides a one-dimensional (1D) view of the heart or great vessels; (2) real-time or sector scanning, in which a two-dimensional (2D), dynamic view is produced; and (3) Doppler ECHO, a technique to quantify blood flow velocity and direction and estimate intravascular pressures. The ejection fraction and wall motion symmetry of the LV can be adequately evaluated, but RV performance is less reliably assessed because of its irregular (noncylindrical) geometry. Color kinesis (color flow) aids in regional wall motion assessment and in determining reflux across valvular structures. Transesophageal echocardiography (TEE) provides very high-resolution images of previously difficult-to-examine regions of the heart and has given good cardiac images in patients in whom transthoracic (surface) ECHO is severely limited (e.g., obese, hyperinflated). ECHO is noninvasive, inexpensive, rapidly performed, and diagnostic in a wide variety of valvular, myocardial, and pericardial disorders. Ambiguity, limited resolution, and interpreter error are its most important limitations. Inferences regarding three-dimensional (3D) structures (e.g., ejection fraction) are made from data collected in 2D format. Because the ultrasound signal is attenuated by fat and reflected by air-tissue boundaries, transthoracic ECHO is of limited value in patients with obesity or obstructive lung disease. Chest wall deformities, dressings, and occlusive coverings often prevent optimal transducer positioning. TEE may require ventilatory support in patients with cardiorespiratory failure. Skilled technical support and an experienced interpreter are essential for optimal results.

*Types of Echocardiogram*
M-Mode Echocardiography

M-mode ECHO provides a 1D “ice pick” view through the heart, forming images from sound reflected along the narrow axis of the beam. M-mode examines the movements of a well-defined tissue core over time. It is well suited to detecting subtleties of motion, such as those needed to detect the severity and significance of impaired ventricular relaxation (“diastolic dysfunction”). Broad structures lying perpendicular to the ECHO axis reflect are well delineated by the acoustic beam. The anterior and posterior ventricular walls, intraventricular septum, aortic root, and valve leaflets (particularly the anterior mitral valve) are represented clearly. Conversely, the pulmonic and tricuspid valves are more difficult to visualize. Consequently, thickening, vegetations, or abnormal motions of the aortic and mitral valve are frequently detected, whereas those of the pulmonic or tricuspid valves are often missed. Because only a single axis or view can be obtained at any particular instant, M-mode is distinctly inferior to real-time 2D ECHO for detecting valve or wall motion abnormalities. M-mode usually allows accurate measurement of selected chamber dimensions, but its narrow sampling window may not accurately reflect the anatomy of the entire atrium or ventricle. Similarly, loculated pericardial effusions, pleural fluid collections contiguous to the pericardial surface, and small intraventricular defects may be missed entirely. An important use of M-mode is to determine IVC dimensions and their variation with the phases of the tidal cycle. Such information may be useful in gauging preload adequacy. Collapsibility of the IVC (during spontaneous breathing) and/or of the SVC during the inspiratory phase of positive pressure ventilation correlates well with the responsiveness to a fluid challenge (see above).

Two-Dimensional Echocardiography

2D (real-time) ECHO is the best technique for examining ventricular wall and valve motion. Because 2D ECHO provides a wider field of view than M-mode, any process localized to a segment of the pericardium or myocardium is better seen (e.g., loculated pericardial fluid, small ventricular septal defects, segmental ischemic wall motion abnormalities, and small LV aneurysms). Diastolic as well as systolic performance of the left heart (and to a lesser extent, the right heart) can be evaluated. Color-flow Doppler allows assessment of the directionality of blood flow across valves (red for movement toward and blue for movement away from the probe). This display provides a vital advantage when assessing valvular performance (Fig. 2-15). 2D ECHO is an invaluable technique for assessing the relative performance of the two ventricles, and when a regurgitant tricuspid leak is present, as it very often is when the RV is abnormally overloaded, the PA pressure can often be accurately estimated. Emergency echocardiographic assessment can be invaluable when doubt exists concerning the cause of abrupt-onset hypotension and/or cardiac arrest. Massively dilated RV and central PA, for example, may provide an important clue to pulmonary embolism as the cause and may prompt the use of thrombolytics.
Intravenous optisonic contrast improves the chamber definition and allows the determination of anatomy with sufficient precision to identify septal defects (as will agitated saline). The regional wall motion abnormalities of recent or remote myocardial infarction are well defined. Chamber dimensions and wall thickness are readily assessed. Ischemic and infarcted areas contract with less vigor and are rather easily detected, allowing the ECHO to functionally image the heart during pharmacologic stress testing. Superior resolution and the ability to delineate valve motion make 2D ECHO superior to M-mode ultrasound for examining right-sided cardiac valves and for detecting mitral prolapse and vegetations. 2D ECHO is also the preferred technique for calculation of valve area. In recent years, the value of ECHO in assessing the relative filling of the central circulation has been emphasized.

**Transesophageal Echocardiography**

TEE uses a miniature ultrasound transducer inserted into the esophagus via an endoscope to obtain high-resolution echocardiographic images. Although TEE is limited by the need to perform endoscopy, it frequently reveals the details of valvular motion, diastolic left heart function, chordae abnormalities, and small valvular...
vegetations missed by surface ECHO. TEE imaging is an accurate means of diagnosing aortic dissection, atherosclerosis, and aortic trauma. It is more reliable than transthoracic 2D ECHO for this purpose. TEE also offers advantages in patients with a body habitus that prevents surface echocardiographic imaging, most notably patients with obesity and hyperinflation of the chest.

**Doppler Echocardiography and Aortic Flow Estimation**

Doppler ECHO deduces velocity of moving blood by interpreting changes in the frequency of reflected sound waves. Either M-mode or 2D ECHO can be used in conjunction with Doppler technology to estimate CO or flow across a valvular orifice. Once valve area is determined and blood velocity is known, flow may be calculated. In many (but certainly not all) patients—those with detectable tricuspid regurgitation—PA pressure can also be estimated. Thus, Doppler potentially provides a means for estimating CO noninvasively. Pressures in various cardiac chambers may also be inferred from Doppler flow estimates. Finally, as already noted, color-flow Doppler helps to detect the regurgitant jets of blood characteristic of valvular insufficiency and abnormal communications between structures (e.g., atrial septal defect).

Esophageal Doppler monitoring of aortic blood flow has been investigated and perfected over the course of more than three decades as a means by which to track changes in CO by interrogating the descending aorta. Miniaturized probes that are intended for continuous use at the bedside are now commercially available. Whatever their limitations for precise quantitation of CO may be (see earlier discussion), their ease of use—even by nurses and other relatively untrained operators—holds significant promise as a noninvasive means for detecting and promptly addressing hemodynamic deterioration.

**Specific Diagnostic Problems**

**Intravascular Volume and Cardiac Filling**

Certain 2D ECHO findings reliably indicate relative overdistention of the RV (e.g., D-shaped septum), whereas others such as ventricular walls that touch during systole or inspiratory collapse of the IVC reflect serious volume depletion.

**Investigation of Pericardial Effusion and Tamponade**

Investigation of pericardial effusion and tamponade is a common use of ECHO in the ICU. Although optimal studies may detect effusions of 25 to 50 mL, delineation of such small pericardial effusions can be fraught with difficulty, especially when pleural effusions coexist. Normally, the epicardium and pericardium are closely apposed, with only slight separation occasionally seen in systole. Accumulated pericardial fluid separates these two structures throughout both phases of the cardiac cycle. Small amounts of fluid in the pericardial sac pool posteriorly in supine patients can be easily missed. 2D is superior to M-mode ECHO for detecting small amounts of pericardial fluid. In such cases, visualizing the LA may be revealing. Pericardial fluid rarely accumulates behind the LA for anatomic reasons. When larger effusions accumulate, diagnosis becomes much easier, as fluid collects anteriorly as well as posteriorly in the pericardial space. When pericardial effusions become very large, the heart may swing to and fro within the sac, producing artifactual wall motion and apparent abnormalities of mitral and tricuspid valve function. The diagnosis of pericardial effusion is commonly missed by ECHO when there is fibroadesive pericardial disease, simultaneous pleural effusion, or massive LA enlargement. The diagnosis of tamponade is a clinical one that cannot be made solely by ECHO criteria. Tamponade physiology may be suspected, however, when a large pericardial effusion is present or when the RA or ventricular cavities show intermittent collapse. Evidence of decreased flow through the mitral valve during inspiration and relatively enlarged RV dimensions are also suggestive.

**Paradoxical Embolism**
ECHO may also be used in the ICU to detect intracardiac shunts in patients with refractory hypoxemia or suspected paradoxical embolism. In such cases, the contrast injected is either an ECHO dense dye or (more commonly) an intravenous fluid containing microbubbles (e.g., agitated saline, sonicated 5% human albumin). In such testing, the acoustic contrast agent is introduced by vein while the ECHO transducer probes the left heart chambers. If a right-to-left cardiac shunt is present, there is prompt appearance of acoustic noise in the LA or ventricle shortly after injection. The legs are preferentially used for such injections because RA streaming patterns favor crossing of the contrast material into the left heart. Although this “bubble” technique has relatively high specificity for right-to-left shunt, it lacks the sensitivity of angiographic dye injections. The sensitivity of TEE substantially exceeds that of surface techniques for detection of intracardiac shunts.

**NUCLEAR CARDIOLOGY**

With the rise of cardiac catheterization, interventional angiography, MRI, multidimensional CT scanning, and increasingly sophisticated ECHO, nuclear medicine techniques now hold a very limited and progressively tenuous place for imaging the heart in critically ill patients. Ventricular size, contour, and segmental wall motions may be assessed. Unfortunately, RVG must be performed outside the ICU, necessitating patient transport.

**SUGGESTED READINGS**


Chapter 3
Shock and Support of the Failing Circulation

• Key Points

1. Circulatory insufficiency and shock result from inadequate perfusion relative to tissue demands. Although certain physical and laboratory parameters may be suggestive, shock is best defined by overt dysfunction of key vital organs—not by parameters that selectively reflect either oxygen supply or demand.

2. Attention to the demand side of the perfusion imbalance is a potent and often overlooked means of reversing the pathophysiology of shock.

3. Early goal-oriented resuscitation may be crucial in deciding outcome, but a pathogenic inability of the mitochondria to utilize available oxygen can limit the effectiveness of hemodynamic interventions.

4. Three basic mechanisms may cause or contribute to circulatory insufficiency: pump failure, insufficient vascular tone (vasoplegia), and hypovolemia. Heart rate and rhythm as well as the determinants of stroke volume (preload, contractility, and afterload) should be considered independently for their potential to contribute to cardiovascular dysfunction.

5. The parameters that characterize heart function must be scaled to body size; any specific value of cardiac output, oxygen consumption, or vascular resistance may take on different significance for large and small patients.

6. During shock, the respiratory muscles may outstrip the heart's ability to deliver adequate blood flow to them. Mechanical support may relieve the ventilatory burden, thereby increasing the blood flow available to other marginally perfused organs.

7. Repeated examination of mental status, urine output, and skin perfusion provides information essential in guiding therapy. Functional monitoring by noninvasive means as well as by arterial, central, and pulmonary artery catheters provides the data necessary to wisely select and regulate the rates of volume and drug infusions.

8. Adequate circulatory volume must be assured whenever vasopressors are used. Fluid type and dosing should be selected by considering the need for blood, the nature of the fluid lost from the vascular space, the acuity of the problem, the urgency of reversal, the financial cost, and the potential risk of the product to the patient.

9. Most (but not all) vasoactive agents used to support the circulation are catecholamine derivatives with $\alpha$, $\beta_1$, or $\beta_2$ activity, in varying proportions. The relative intensity of each effect varies with dosage.

10. Mechanical interventions (ventilatory support, positive end-expiratory pressure, aortic balloon pumping, venoarterial extracorporeal membrane exchange [ECMO]) may be needed to reduce afterload or modify preload. Once initiated, these interventions should be maintained only as long as necessary but should be withdrawn cautiously.

PHYSIOLOGY OF THE FAILING CIRCULATION

Circulatory Insufficiency—Decompensated Congestive Failure and Shock

The term congestive heart failure (CHF) indicates limited or exhausted pumping reserve and elevated cardiac filling pressures that promote dyspnea. During decompensated CHF, discussed in the second part of this
chapter, dyspnea is usually present at rest but organ perfusion typically is well maintained until reserves are stressed by exercise or other metabolic demands. The term “shock” indicates an immediately life-threatening inadequacy of perfusion relative to tissue demands at rest and may or may not imply heart dysfunction. Although certain physical and laboratory parameters are characteristic, shock is defined by overt dysfunction of vital organ systems—not uniquely by such “supply side” parameters as blood pressure (BP) or cardiac output (CO) or by such “demand side” parameters as oxygen consumption (VO₂). What might be considered a normal CO in a healthy subject at rest may inadequately perfuse the tissue beds of a critically ill patient with maldistributed blood flow or high metabolic demands. The prime objective of circulatory support, therefore, is to maintain near-optimal vital organ perfusion, as reflected in mental status, urinary output, systemic pH, and lactate concentration, at acceptable cardiac filling pressures. Local organ perfusion is governed by its driving pressure and vascular resistance. Ordinarily, an adequate pressure gradient is present, and vasomotor tone regulates individual organ perfusion in proportion to its metabolic demand. Under resting conditions, only a small percentage of all vascular channels is fully open. However, when the available pressure fails to maintain adequate flow despite optimized vasomotor tone (e.g., during a cardiovascular crisis or hypovolemia) or when defective vasoregulation fails to maintain perfusion pressure or flow distribution (e.g., during sepsis), vital tissues are not adequately nourished to maintain all normal cellular functions. The vascular beds of different organs vary in the extent to which they can compensate for deprivation of normal regional blood flow and/or drop in circulatory pressure. Certain conditions, such as sepsis, may interfere with these delicate vasomotor controls and eventually with innate mitochondrial function. The shock syndrome is initiated when these compensatory mechanisms reach their limits. Once shock physiology is under way, vasoactive mediators and products of inflammation, some with myocardial depressant properties, may be released into the circulation system to perpetuate the circulatory crisis. Even with appropriate treatment, mortality remains high for septic shock and for cardiogenic shock unaddressed by coronary reperfusion.

**Determinants of Cardiac Output**

Although attention usually is focused on the pump that energizes the circulation (the heart), vascular compliance and tone are equally important. Thus, whereas the Frank-Starling relationship offers a useful if somewhat restricted perspective on global circulatory kinetics, CO can be viewed equally well as a function of the effective pressure gradient driving blood from the periphery back to the heart and the resistance to venous return. The average upstream peripheral force driving venous return, the mean systemic pressure (MSP), is the equilibrium pressure that would exist throughout the vasculature if the heart abruptly stopped pumping (see Chapter 1). Because of the large capacitance of the venous relative to the arterial bed, MSP (normally 7 to 10 mm Hg) lies much closer in value to the central venous pressure (CVP) than to mean arterial pressure (MAP). MSP is influenced by both blood volume and vascular tone. Early in many shock states, aggressive filling of the vasculature is often required to compensate for the vasoplegia that otherwise would cause MSP to fall. Capacitance beds must be adequately filled and the vasculature appropriately “stressed” before vessel tone and MSP can rise to adequate levels. (Vigorous and prompt resuscitation of the intravascular compartment with fluids and pressors helps account for the reported success of early “goal-directed therapy.”) The downstream back pressure to venous return is right atrial pressure (P_RA). If MSP fails to rise sufficiently to compensate for an increase in P_RA, CO falls. Indeed, the relationship between CO and P_RA is linear for any specific value of MSP, and the slope of this relationship is influenced by the resistance to venous return. The tendency of the vena cava to collapse limits the extent to which effective driving pressure (MSP - P_RA) can be increased by reducing P_RA.
The actual CO observed at any moment is defined by the intersection of Starling and venous return curves. Thus, both pump factors (heart rate [HR], loading conditions, and contractility) and circuit factors (intravascular volume, vessel tone) influence circulatory performance. Three basic mechanisms may cause or contribute to circulatory failure: (1) pump dysfunction, (2) insufficient vascular tone, and (3) hypovolemia.

**Pump Failure**

**Heart Rate**

CO, the product of HR and stroke volume (SV), can be depressed by abnormalities of either variable (see Chapter 1). To meet metabolic demand, isolated abnormalities of either SV or normally can be offset by adjustments in the other over a wide range. Both extremes of HR may cause CO to fall to shock levels. During sinus rhythm, the maximal sustainable physiologic HR can be estimated as $(HR_{\text{max}} = 220 - \text{age})$. Sinus HRs that exceed this value may compromise CO and myocardial perfusion, even in healthy individuals. When the heart is noncompliant or compromised by coronary insufficiency, CO may fall at considerably lower HRs. Furthermore, the loss of atrial contraction that accompanies many tachyarrhythmias (i.e., atrial fibrillation) may depress CO on this basis alone. Conversely, when diastolic dysfunction is the primary problem, deliberate slowing of HR by beta blockade lengthens filling time and helps relieve congestion.

**FIGURE 3-1. Regulation of CO.** CO is determined by the intersection of the Frank-Starling and venous return curves. Venous return, which is driven by the difference between MSP and CVP, tends to improve as CVP falls, until the point at which venous pressure is insufficient to prevent vessel collapse (arrow). For the same venous return curve, the failing heart reduces its output, despite a higher filling pressure. CO can be maintained at a nearly normal level by increasing intravascular volume and/or using an inotrope or afterload reducer. Hyper and
Hypo relate to volemic status (Hypervolemia, Hypovolemia).

In the intensive care unit (ICU), hypoxemia, enhanced vagal tone, and high-grade conduction block caused by intrinsic heart disease or pharmacologic agents are key mechanisms causing bradycardia. The normally compliant and contractile ventricle can adapt to physiologic or pathologic depressions in HR via the Starling mechanism; for example, young, well-conditioned athletes often maintain resting HRs less than 40 beats/min. However, patients with impaired myocardial contractility or reduced effective compliance (e.g., ischemia, diastolic dysfunction, pericardial disease) may not be able to mount a compensatory rise in SV and suffer depressions in CO and BP when HRs fall into the low normal range (<50 beats/min). This is especially true when the normally coordinated activation sequence is compromised (e.g., atrial fibrillation, left bundle branch block) or metabolic demands are high. Because bradycardia lengthens diastole as a proportion of total cycle time, MAP sinks closer to the diastolic value as HR slows. Perfusion of the heart and other key organs may suffer. It must be remembered that the appropriate physiologic response to hypovolemia is sinus tachycardia; hypotension suspected on the basis of massive gastrointestinal (GI) hemorrhage, therefore, should be accompanied by a compensatory tachycardia. A normal HR in this setting implicates an erroneous diagnosis or superimposed vagal, drug, or pathologic explanations.

**Stroke Volume—Loading Properties and Contractility**

SV is determined by end-diastolic volume and ejection fraction. End-diastolic volume, in turn, is the product of transmural filling pressure and myocardial compliance. As discussed in Chapter 1, SV and CO are often well preserved despite florid cardiogenic pulmonary edema. The myocardial hypertrophy of chronic hypertension or aortic stenosis, or the functional ischemia of coronary disease can result in symptomatic diastolic dysfunction. In such cases, control of hypertension, reduction of HR, coronary vasodilation by nitrates, and/or reducing systemic O\(_2\) demand accelerate recovery and help prevent symptomatic recurrence.

Foremost among the primary depressants of contractility and ejection fraction during critical illness are (1) acute ischemia; (2) extensive myocardial necrosis; (3) humoral mediators (collectively known as “myocardial depressant factors”) released during inflammation and trauma; and (4) drugs that impair contractility (e.g., nonspecific β-blockers, calcium channel blockers, and antiarrhythmics—most notably of the type la class). Cardiogenic shock consequent to acute myocardial infarction implies cumulative losses exceeding 40% of the total myocardial mass.

Severe cardiac dysfunction may arise abruptly from “stress cardiomyopathy” (known by other names such as “Takatsubo,” “apical ballooning,” or “broken heart” syndrome). This reversible ischemic condition originally was thought to affect primarily women under severe emotional or physical stress. Although no coronary occlusion or marked myocardial necrosis is present, contractile dysfunction of the mid portion and apical regions of the left ventricle may be severe enough to cause severe hypotension. Key features of this condition are now recognized to complicate critical illnesses of other populations and etiologies, presumably mediated by mitochondrial injury, microvasoconstriction, and catecholamine excess. The prevalence and consequences of such pathophysiology argue strongly for moderation in the use of adrenergic drugs so as to avoid excess stimulation of catecholamine bioreceptors. Supportive care and avoidance of catecholamine stimulation is the current standard of care. It is not rare, however, for aggressive support by intra-aortic balloon pump (IABP) to be required. Resolution may require weeks after initial presentation.

Structural defects, such as papillary muscle rupture or postinfarction ventriculoseptal defect (VSD), may compromise CO on a mechanical basis, even when there has been subcritical myocardial damage. Because the output of a failing heart is influenced by the impedance to ventricular ejection (afterload), increased vascular tone may improve BP at the expense of tissue perfusion. Patients with “tight” aortic stenosis are especially sensitive
to changes in preload and contractility.

To scale for metabolic needs, the CO must be referenced to body surface area. The resulting quotient, the
cardiac index (CI), attempts to take the mass of metabolizing tissue into account (normal >2.5 L/min/m²). CO
adequacy can be judged only with respect to metabolic demands. Under some circumstances, even a normal CI
may be insufficient for vital organ support. Such “high-output” cardiac failure can be precipitated by fever,
anemia, thiamine deficiency, thyrotoxicosis, and arteriovenous shunting. Patients with extensive burns, severe
sepsis, or cirrhosis also may have vastly higher CO requirements than the average resting patient.

**Failure of Vascular Tone**

Because organ perfusion depends on the gradient of pressure and the resistance to flow through its tissue bed,
vasodilation and/or impaired distributive control may produce the shock syndrome, even when the CI is
maintained within the normal range. Early sepsis provides a common example of maldistributive shock,
characterized by reduced afterload and normal or elevated CO and VO₂, despite undernourished vital tissue
beds. General and spinal anesthesia, autonomic failure resulting from acute spinal cord injury, anaphylaxis,
sedatives, and drugs such as propofol may also produce generalized, nonselective vasodilation that leads to
underperfusion of critical organs, especially in the presence of hypovolemia. The inability to produce sufficient
glucocorticoid (cortisone), not uncommon in critical illness (relative adrenal insufficiency), suppresses both
vasomotor tone and myocardial contractility.

The therapy of shock states often focuses on maintaining a BP targeted to the physiology of the patient in
question. This is an appropriate orientation, considering that the cerebral and coronary vasculatures (and to a
lesser extent that of the kidney) are critically dependent on their perfusion gradients and relatively unaffected by
the drug-induced vasoconstriction experienced elsewhere. Moreover, during the vasoplegia of sepsis the
maintenance of adequate MAP determines perfusion and washout through other tissue beds, as well. It must be
emphasized that adequate BP and adequate flow are not synonymous; vasoactive drugs may cause intense
ischemia of “nonvital” vascular networks (gut, muscle, skin), occasionally with serious consequences for overall
outcome.

Although moderate acidosis is generally well tolerated, severe metabolic acidosis may aggravate the shock state
by causing myocardial depression, catecholamine resistance, increased right ventricular afterload, and
potentially irreversible precapillary arteriolar dilation. Selective arteriolar dilation produces direct cellular injury
and massive transudation of fluid into the extracellular spaces. Adrenal insufficiency and (less commonly)
myxedema are two frequently overlooked endocrine problems that may contribute to vasomotor dysregulation
and circulatory failure.

**Hypovolemia**

Although inadequacy of circulating blood volume is in itself a primary cause of circulatory failure, a

*relative* deficiency of intravascular volume often contributes cause in the setting of impaired pump function or
reduced vascular tone (e.g., sepsis). Primary hypovolemic shock develops during hemorrhage or when extensive
extracellular volume losses result from burns, pancreatitis, vomiting, diarrhea, anaphylaxis, hypoproteinemia, or
multiple traumas. Right ventricular infarction and pericardial disease mimic the tachycardia and low pulse
pressure of hypovolemia despite systemic venous congestion and/or normal wedge pressure because they
impair left ventricular (LV) compliance.

**Cardiodepression and Electrolyte Disturbances**

Contractility of myocardium and vascular smooth muscle can be adversely influenced by nonphysiologic
concentrations of key electrolytes, especially when several disorders are encountered simultaneously. Hypermagnesemia and hyponatremia occasionally are the primary causes of difficulty but usually serve a secondary role. The most frequent underlying causes of cardiovascular depression are hyperkalemia and, more rarely, deficiency of ionized calcium. An approach to the diagnosis and management of these disorders is provided in Chapter 13.

Pharmacologic Effects
Although all antihypertensive drugs may evoke hypotension, two commonly used classes of therapeutic agents—calcium channel blockers and β-blockers—directly interfere with cardiac function and may either exacerbate congestive heart failure (CHF) or encourage cardiovascular collapse. The appropriate response to excessive calcium channel blockade is to administer sufficient calcium to counter the drug's adverse effect; either the chloride or gluconate salt can be given as a bolus. Calcium chloride can be administered by continuous infusion as well. Catechol-based vasopressors and inotropes are indicated in addressing hypotension, but all may prove ineffective until calcium channel blockade is overcome. High-dose insulin (1 to 10 units/kg/h) has shown promise in both clinical and experimental toxicology environments when care is taken to keep glucose and potassium concentrations within normal limits.

β Blockade
Through actions on myocardial contractility, HR, bronchodilation, alveolar liquid clearance, and peripheral vasodilation, stimulation of one or more subtypes of β receptor is of fundamental importance to the recovery of the acutely compromised circulation. By influencing these properties, β-blocking drugs have unquestioned utility in managing a range of cardiovascular problems arising in the acute care setting, including ischemic cardiovascular disease, tachycardia, hyperthyroidism, aortic dissection, diastolic dysfunction, and acute hypertensive crisis. Whereas the use of well-selected β-blocking drugs is appropriate to the management of specific disorders that require such intervention, they should be withheld from the care of acutely ill patients in the absence of firm and specific indications (acute myocardial ischemia, symptomatic tachyarrhythmia, etc.). Currently, β-blocking drugs are frequently used in the outpatient setting not only for hypertension and rate control of atrial arrhythmias but also to address diastolic dysfunction or chronic CHF (where they may help adaptive remodeling). Routine use of β-blockers, although partially justified by outcome studies of selective β-blockers in large populations, may backfire during periods of stress (e.g., sepsis, myocardial infarction, dietary indiscretion), especially in the elderly. The β-blocking drug already “on board” then accentuates hypotension or contributes to “flash pulmonary edema” by interfering with the limited compensatory responses of these patients with compromised cardiovascular reserve. Certain long-acting, nonselective, and inexpensive β-blockers (e.g., atenolol) are especially problematic, in that native drug and/or active metabolites are renally excreted and therefore accumulate during prerenal azotemia. While it is generally agreed that initiating β-blockade is hazardous for a patient already in decompensated congestive failure or shock, the wisdom of continuing β-blocking drugs during an acute episode of decompensation should be considered on a case-by-case basis. Whereas withdrawal of the drug might help forward output, certain salutary effects of the β-blocking drugs (HR, rhythm, myocardial compliance) are foregone. Patients who are acutely volume overloaded with preserved BP and appropriate renal function (“warm and wet”) usually tolerate continuation of outpatient doses. On the other hand, hospitalized hypotensive patients with marginal perfusion and renal insufficiency unresponsive to diuretics should in most cases have their dose initially decreased by half and further reduced if decompensation does not quickly resolve. Acute complete stoppage of the chronic β-blocker is undertaken primarily for contraindications such as heart block and severe refractory shock. The approach to managing life-threatening β receptor blockade (overdose) is similar to that for calcium channel blockade: high-dose insulin may be considered if β-stimulants, vasopressin, and glucagon prove
inadequate to reverse shock.

**Effect of Shock on Organ Function**

The closely autoregulated central nervous system of the healthy subject can tolerate marked reductions in MAP (to 50 to 60 mm Hg) without sustaining irreversible tissue damage. However, cerebrocortical functions are among the first to be impaired as shock develops. Higher MAP targets are required in patients with chronic hypertension or vascular disease.

As a rule, serious reductions of MAP are tolerated poorly by the GI tract. Early in shock, the gut suffers marked reductions in flow. This flow reduction eventually impairs mucosal function and bowel integrity, occasionally to the point of frank ischemic necrosis. A reduction of gastric mucosal pH is among the first indications of inadequate gut perfusion. One popular paradigm suggests translocation of gut bacteria, their products, or debris across the abnormally permeable gut mucosa and into the lymphatic system or bloodstream as the next step on the path to multisystem organ failure. Hepatic ischemia may elevate liver function tests, alter the metabolism of drugs, and impair removal of toxins, lactate, and coagulation products.

Shock often impairs the clotting system sufficiently to initiate disseminated intravascular coagulation (DIC). The stimulus is multifactorial, and the important contributing factors are vascular endothelial injury, cell death, and impaired hepatic clearance of fibrin degradation products (see Chapter 30). In response to hypotension, the kidneys secrete renin to retain sodium and water. Intense vasoconstriction of the afferent arterioles shunts blood from the cortex to the medulla, reducing glomerular filtration to a greater degree than total renal blood flow or CO. If profound or prolonged, underperfusion may culminate in acute tubular necrosis. Antidiuretic hormone released from the pituitary helps conserve water and may contribute to hyponatremia.

During protracted shock and immobility, the skeletal muscles may release sufficient quantities of myoglobin into the circulation to impair renal tubular function (rhabdomyolysis). The hyperpnea that accompanies profound hypotension requires the respiratory muscles to consume large quantities of oxygen, outstripping the heart's ability to deliver adequate flow to them, and ventilatory failure may result. Intubation and mechanical ventilation during circulatory shock decrease respiratory muscle $O_2$ consumption, thereby increasing the blood flow available to other critical organs. Thus, in the vigorously breathing patient, mechanical ventilation often improves circulatory homeostasis.

**Evaluation of Perfusion Adequacy**

The history, physical examination, laboratory tests, and ancillary tests form the core of the evaluation process of the patient with circulatory inadequacy (Table 3-1). The clinician should rapidly undertake a targeted history, with review of prior vital signs and recent events and/or interventions that led to the shock state. Special attention is paid to preexisting illness and the medication listing. Key features of the physical examination include otherwise unexplained alterations of vital organ function (mental status, urine output); hypotension relative to the usual baseline; sluggish capillary refilling; and cool, clammy skin. Neck vein examination and cardiac auscultation are essential focus points, keeping alert for signs of isolated right ventricular failure. Electrocardiogram (and in most cases echocardiogram) should be obtained in shock that is not of obvious cause or that does not reverse easily. Bedside ultrasonic imaging of the great vessels and heart provides invaluable diagnostic information. Laboratory tests that reflect cardiac dysfunction (troponin, brain natriuretic peptide [BNP]) and/or perfusion inadequacy (anion gap, lactate) are often worth repeating as therapy progresses. Relative adrenal insufficiency is common enough to warrant measurement of serum cortisol concentration and its response to stimulation, especially in those refractory to intravenous fluid and vasopressor resuscitation. Arterial blood gas and central venous oxygen saturation data are sufficiently
valuable that insertion of catheters should be considered to provide for their serial monitoring.

### Table 3-1. Vital Database in Hypotensive States

**CLINICAL HISTORY**
- Past medical history and baseline vital signs
- Recent interventions and events

**PHYSICAL EXAMINATION**
- Vital signs
- Urine output
- Skin temperature and character
- Capillary refill time
- Neck veins/cardiac auscultation

**LABORATORY TESTS**
- Arterial blood gases
- Central venous $O_2$ saturation
- Hemoglobin/hematocrit
- Anion gap
- Lactate
- Brain natriuretic peptide
- Cortisol
- Troponin

**ANCILLARY INFORMATION**
- Radiographs chest and abdomen (when indicated)
- Electrocardiogram
- Echocardiogram
- Vascular ultrasound
- Bladder pressure
- Noninvasive cardiac output

### THERAPY OF CIRCULATORY SHOCK

**Goal-Directed Therapy**

Because prolonged hypoperfusion leads to sustained organ failure and irreversibility, most experienced clinicians agree that shock should be reversed as quickly as feasible to safely do so. Early aggressive intervention to restore an effective circulation has become an accepted goal, even if the precise target at which to aim is debated. During the initial resuscitation phase of sepsis, at least 30 mL/kg of fluid should be given over the first 3 hours of care, targeting a minimum MAP in most patients of greater than 65 mm Hg and a falling lactate serum level. Two elements seem important: early intervention and restoration of adequate perfusion to vital organs. What measurable indicator is the most logical to shoot for? Generally speaking, supranormal values for CO and oxygen delivery are neither easy to achieve nor advisable. Restoring near-normal values for central venous $O_2$ saturation, though actively debated, is thought prudent by many clinicians, based on the persuasive results of an important prospective clinical trial. The central venous saturation reflects the ratio of $O_2$ delivery to consumption.
Targeting a central venous saturation of greater than 70% has been associated with higher survival than use of an MAP target. Unlike the mixed venous $O_2$ saturation, central venous sampling can be readily achieved via routine central lines as well as monitored continuously via specialized catheters. As a helpful but not infallible indicator of perfusion adequacy, central venous $O_2$ saturation should be considered a valuable complement to routine arterial pressure monitoring.

**Indications for Monitoring**

Repeated examinations of mental status, urine output, and skin perfusion provide information essential in guiding therapy. MAP normally exceeds 90 mm Hg. Although no specific BP should be used as the sole endpoint of circulatory support, an MAP of 60 to 70 mm Hg is required for most patients to perfuse the heart, brain, and kidneys adequately; higher pressures are required in those with vascular disease and/or long-standing hypertension prior to presentation. The catchphrase for all types of quantified observation is *functional* monitoring. Absolute values for any hemodynamic parameter take a back seat to the response of the target variable to intervention.

Arterial and ventricular filling pressures should be monitored continuously when hypotension produces signs of vital organ dysfunction that are not readily reversed. For young patients without underlying heart or lung disease, a CVP catheter may suffice to monitor filling pressures. The central venous oxygen saturation is an overlooked and potentially valuable indicator of perfusion adequacy in the setting of hypovolemic or cardiogenic shock. When Doppler-aided echocardiography, vascular ultrasound, and radiographic imaging leave doubt as to appropriate management or the patient remains hemodynamically unstable, the placement of a pulmonary arterial catheter, which aids in accurate assessment of LV filling pressure, CO, and mixed venous oxygen saturation on an ongoing basis (see Chapter 2), may be considered. By enabling calculations of vascular resistance indices, pulmonary artery (PA) catheters can be helpful in diagnosing the etiology of shock and in guiding therapy. Although a PA catheter clearly is *not* indicated in all, it is of value in many circumstances, and most hypotensive patients requiring vasopressor support should be monitored invasively via arterial catheter. Severe peripheral vasoconstriction and the reduced pulse pressure of certain shock states make determination of systemic BP by standard cuff methods difficult and unreliable. Arterial catheterization allows frequent determinations of blood gases, effortless blood drawing when other sites prove difficult or are unavailable, and continuous assessment of BP. A bladder catheter also should be placed in patients with hypotension to monitor urine output as an index of renal perfusion and adequacy of $O_2$ delivery. Consideration should be given to carefully measuring bladder pressure (an indicator of intra-abdominal pressure) when the possibility of an ongoing or developing abdominal compartment syndrome is entertained.

**Fluid Therapy**

Water normally constitutes about 60% of body weight. Of this total, approximately two thirds is intracellular and approximately one third is extracellular (Fig. 3-2). Of the extracellular fluid, one quarter is intravascular and three quarters is interstitial. Isotonic solutions (e.g., normal saline and Ringer balanced salt solution) initially distribute primarily into the extracellular space, whereas the distributive space of hypotonic (or potentially hypotonic) fluids approximates that of total body water. Therefore, hypotonic fluids (e.g., one-half normal saline) or fluids subject to rapid metabolism of their osmotic components (e.g., D5W) only affect intravascular volume transiently (only one twelfth of the volume of D5W remains intravascular after dextrose metabolism). As a result of normal fluid
partitioning, replacing a specific volume of lost plasma requires at least four times as much isotonic crystalloid and even more hypotonic fluid. Because two thirds of isotonic crystalloid enters the interstitial space within 60 minutes of its administration, edema should be expected after massive fluid resuscitation with crystalloid. Although the resulting tissue edema is generally thought to be well tolerated, the lungs as well as the peripheral tissues are affected. After rapid and massive resuscitation, a compartment syndrome can develop in an extremity or in the abdomen, especially in those who have undergone profound and sustained ischemia.

![Body fluid distribution in normal healthy adult.](image)

When first given, large volumes of fluid initially dilute the packed cell volume (PCV) and serum proteins. As fluid redistributes out of the vascular space, these values tend to return gradually toward their preinfusion baselines. The time required for this equilibration or “circulation dwell time” is brief for crystalloid. Redistribution begins within minutes and is completed within hours.

Both enthusiasm and caution have been expressed for the use of hypertonic saline in initial resuscitation efforts. Hypertonic saline has volume-expanding, vasodilating, and possible immune modulating effects. Once it is given, BP may stay elevated for several hours before its effect dissipates, and it is clearly effective in treating some forms of intracranial hypertension. Few serious side effects have been reported, but adverse consequences from
rapid intravascular volume expansion and pulmonary edema remain a concern. Its use is not advised beyond the initial stabilization phase of management. Clinical comparison trials have demonstrated its utility in hemorrhage-associated severe hypotension and perhaps even a survival advantage in that setting. However, no convincing survival benefit has been shown for most settings of life-threatening shock.

Hypotension complicated by renal insufficiency or anuria presents a difficult challenge that requires skillful management. Dialysis often is required for these patients to clear toxins, restore electrolyte balance, allow nutritional support, and offset metabolic acidosis. Early dialysis has been suggested (but not proven) to shorten the course to recovery and deserves consideration from the outset of anuria resistant to volume repletion and diuretics. Continuous venovenous or arteriovenous hemofiltration can be especially helpful when fluid overloading or acidosis complicates management, because it allows the gradual removal of sodium and water—a useful aid for oliguric patients who require frequent saline or bicarbonate infusions. Effective dialysis can be performed using similar methodology (see Chapter 29).

**Use of the Fluid Challenge**

Fluid challenge is instrumental for assessing the need for volume replacement in hypotensive patients. In fact, for most hypotensive patients without evidence of pulmonary edema, fluid administration is rarely an inappropriate first response. Although some patients respond transiently to simple leg elevation (the head and chest must be horizontal), such a quick and reversible translocation of volume is a “one time only” maneuver, is generally short-lived, and only serves to indicate potential responsiveness to a volume infusion strategy. Another reversible challenge is to raise or lower the level of positive end-expiratory pressure (PEEP) in those in whom such maneuvers are not contraindicated. Wide respiratory variation of systolic BP or of pulse pressure during controlled ventilation is a helpful indicator (see Chapter 2) of intravascular volume need.

The keys to effective fluid challenge are (1) use crystalloid as the challenge fluid, (2) use a relatively large volume (500 to 1,000 mL) to maximize chances of detecting a significant hemodynamic effect, (3) infuse the fluid rapidly, and (4) closely monitor the patient's response. Because the majority of an isotonic fluid load diffuses into the interstitial space within hours, crystalloid infusions are a relatively “reversible” method for expanding the intravascular compartment. Large volumes of fluid are infused rapidly to maximize the hemodynamic impact before redistribution dissipates the preloading effects. Fluid challenge should not be performed without close monitoring by a clinical caregiver. To obtain meaningful information safely, it is important that physical examination, CVP (or wedge pressure), HR, and arterial pressure be monitored closely. A marked, sustained increase in filling pressure after fluid infusion signals that the heart is operating on the flat portion of the Starling curve, particularly if CO or MAP fails to rise. In such patients, further administration of intravascular fluid may overload the circulation, causing pulmonary edema. Conversely, if the fluid bolus causes small or transient increases in filling pressure that are accompanied by a substantial increase in MAP (and/or CO, when measured) and a stable or reduced HR, fluid administration is likely to benefit.

**Selection of Fluids**

Selection of intravenous fluid is controversial, possibly because all available products have advantages and drawbacks. One logical approach is to replace adequate quantities of the missing constituent. For example, blood replacement is rational to counter severe hemorrhage, whereas isotonic crystalloid is appropriate for the dehydrated patient with near-normal electrolytes. Because of the risks associated with infusions of blood products, and because maintenance of a normal hemoglobin concentration may not benefit perfusion or outcome, transfusions should be carefully considered and their use minimized. Blood is not essential for resuscitation unless there is acute blood loss, marked anemia that is poorly tolerated, and/or ongoing coagulopathy (see Chapter 14). The major difference between colloids and crystalloids resides in the tendency
of the former to remain within the vascular space. Unlike saline, most infused colloids remain intravascular for many hours; it may require as much as five times more crystalloids than colloids to achieve equivalent intravascular volume expansion. However, colloids are expensive, frequently costing many times more than crystalloids to achieve similar volume expansion effects. They are associated with a minor allergic risk, and some impair coagulation. Published studies have not shown a consistent mortality difference between colloids and crystalloids in this setting.

**Crystalloid**

Physiologic “normal” saline is the preferred crystalloid for volume expansion, except in patients with hyperchloremic acidosis, a setting in which saline may worsen the problem. The concentrations of sodium and chloride in 0.9% saline are significantly higher than those in normal plasma (especially chloride), contributing to hypernatremia and hyperchloremia when infused in large quantities, which often give rise to metabolic “acidosis” as bicarbonate must decline to maintain electrical neutrality (see Chapter 12). Ringer solution, although a physiologically balanced fluid, has a slightly lower Na⁺ concentration than does normal saline; therefore, less infused volume remains intravascular. Additionally, it contains 4 mEq/L of K⁺, which is undesirable for patients with renal failure, oliguria, and hyperkalemia. Although the lactate in Ringer solution does not potentiate systemic lactic acidosis, its metabolism to bicarbonate occurs slowly in patients with shock or hepatic hypoperfusion. Hypertonic crystalloid (3%, 7.5%, 15% saline) has been used effectively for emergency resuscitation, and some investigators have infused hypertonic saline continuously over 24 hours for ongoing hemodynamic support. The mechanism of action appears directly associated with volemia, as these solutions clearly help redistribute total body water into the extracellular compartment. Other putative actions of these hypertonic solutions include anti-inflammatory, endothelium-stabilizing, and antioxidant effects. Hypertonic saline risks the development of hypernatremia and hypervolemia, and its proper role in resuscitation continues to be debated.

**Colloid Infusion Options**

**ALBUMIN**

Albumin synthesized by the healthy liver (about 12 g/d), accounts for 80% of the colloid osmotic pressure of plasma and has a half-life of approximately 18 days. Therapeutic albumin is available as 5% (isotonic) or 25% (hypertonic) solutions. Controversial early studies, now largely refuted, suggested a poorly characterized higher mortality rate with albumin use. Recent prospective trials not only have failed to confirm this general contention but suggest that albumin is comparatively efficient as a resuscitation fluid and may effectively complement crystalloids when the latter are given in large amounts. One of the potential reasons for disagreement among clinical studies is that commercially available solutions vary with regard to protein composition, binding capacity, metal ions, antioxidant potential, etc. Undisputed is the fact that isotonic “salt-poor” albumin actually contains up to 145 mEq/L of sodium. The 25% solution delivers relatively less salt per unit of colloid than does its isotonic counterpart and, therefore, may offer an advantage in edematous patients. The oncotic effect of 1 g of albumin is to draw approximately 18 g of H₂O into the vascular compartment. Because albumin leaks gradually from the intravascular space, its circulating half-life in many forms of shock is only about 16 hours. Albumin must not be used as a nutritional supplement for hypoalbuminemic patients (e.g., nephrotic syndrome or hepatic failure). Exogenous albumin is catabolized rapidly or excreted in these conditions, negating its nutritional value and blunting its effect on volume expansion. In unusual circumstances (e.g., anabolism with preexisting hypoalbuminemia, cirrhosis with oliguria, hypoponcotic acute respiratory distress syndrome [ARDS]), the administration of albumin can raise intravascular oncotic pressure for extended periods and should be considered if pulmonary edema is present and refractory to diuretics. On the basis of a subgroup analysis of the influential SAFE trial, hypotonic albumin solutions should not be given to patients with traumatic brain injury.
Whether concentrated albumin carries the same risk is not established. Once a definite risk for transmitting certain viral infections, albumin is now heat treated, and donors are better screened, obviating this hazard. It contains no viable coagulation factors. Albumin is more costly than crystalloid and has been incriminated (but not confirmed) as a potential contributor to morbidity in selected populations. Nonetheless, several definitive clinical trials comparing albumin and crystalloid as replacement fluids demonstrated no convincing advantage or hazard for either option.

**FRESH FROZEN PLASMA**

Fresh frozen plasma (FFP) provides another source of colloid protein. Because FFP carries a significant risk of allergic reaction and potentially risks infection, it should not be used solely for volume expansion. However, when hypovolemia and coagulopathy coexist, FFP may help reverse both. The usual FFP dosing range is 10 to 20 mL/kg, but the need is case dependent.

A variety of synthetic colloids have been developed and introduced to clinical practice. Although each has its adherents and detractors, all have notable deficiencies and iatrogenic potential and therefore continue as subjects of controversy. Particular concerns regarding associated renal stress or injury have plagued their widespread deployment when suitable albumin-based colloids are available and affordable.

**DEXTRAN**

Dextran, a mixture of heterogenous polysaccharides available as 40,000 or 70,000 molecular weight (MW) solutions, is now rarely used. Clearance of small MW fractions occurs rapidly through renal filtration, whereas larger molecules are taken up and metabolized by the reticuloendothelial system. The effect of dextran on circulatory volume is relatively brief, with only 20% to 30% remaining intravascular after 24 hours. Dextran offers several potential advantages: it produces volume expansion greater than the volume infused, promotes “microvascular” flow by coating vessel walls and decreasing red cell-vessel wall interaction, and reduces serum viscosity.

Unfortunately, dextran also has important adverse characteristics. Reductions in platelet adherence and degranulation may incite bleeding, most often when doses exceed 1.5 g/kg/d. If urinary flow is sluggish, renal failure may occur secondary to tubular obstruction. Minor allergic reactions are seen in approximately 5% of cases (patients with previous streptococcal or *Salmonella* infections are predisposed). Fatal anaphylactic reactions occur rarely. The osmotic diuresis that follows dextran resuscitation may necessitate ongoing fluid replacement. Finally, dextran interferes with several common laboratory tests, occasionally producing false elevations of serum glucose, bilirubin, and protein concentrations. Dextran also mimics antibody-induced red cell agglutination, making cross-matching of blood more difficult.

**HYDROXYETHYL STARCH**

Hydroxyethyl starch (HES), a polysaccharide structurally similar to glycogen, is supplied as a mixture of MW fractions from 10,000 to 1,000,000. HES expands plasma volume in direct relationship to the amount infused. Small MW fractions of HES are cleared predominantly by the kidney, whereas reticuloendothelial cells metabolize larger MW fractions. HES is also degraded by serum alpha amylase. Trace amounts of intracorporeal HES have been detected more than 4 months after its administration. Prolonged or massive starch infusion may accumulate in phagocytes, resulting in unknown effects on immune function.

HES prolongs the partial thromboplastin time (PTT) modestly for most patients, but the mechanism is uncertain. HES also causes a transient decrease in platelet count and clot tensile strength. Intracerebral hemorrhage has
been reported in intracorporeal HES recipients. Clotting abnormalities may be reversed with transfusions of FFP and platelets. Allergic reactions occur in less than 1% of patients receiving HES; anaphylactic reactions are extremely rare. HES may artifactually increase the sedimentation rate and often doubles the serum amylase. In a minority of patients, indirect bilirubin may be elevated spuriously by up to 1 mg/dL. HES and 5% albumin are similar in cost, and both are more expensive than dextran.

Given the associated trade-offs detailed, a 5:1 ratio of crystalloid to colloid is sometimes advocated because it provides more effective volume resuscitation than does crystalloid alone at less cost than using colloid exclusively. A crystalloid-containing regimen also helps to replenish intracellular fluid losses.

GELATINS

Gelatins are polydisperse polypeptides produced by degradation of bovine collagen. Although gelatins were long considered not to influence blood coagulation other than by dilution, there is now increasing evidence that gelatins do influence platelet function and blood coagulation. Overall, gelatins appear to be without predictably adverse effects on kidney function. Well-controlled studies on the use of gelatins and their influence on renal function in the critically ill, however, are missing. Gelatins are not commonly available in North America, and their modest and short-lived effectiveness in expanding plasma volume has decreased the initial enthusiasm for this type of colloid worldwide.

In general, crystalloids appear to be just as effective as colloids in the majority of clinical settings, suggesting that the more expensive colloids are overused. However, specific patient populations, such as those with liver disease, those who have edema in conjunction with a low plasma oncotic pressure, and those at high risk of acute renal failure, may benefit from judicious colloid administration.

Vasoactive and Inotropic Drugs

General Principles

The primary goal of vasopressor therapy is to support vital organ perfusion—not to achieve any specific BP. Because vasoactive drugs are relatively ineffective in volume-depleted patients and are partially inhibited in the setting of severe acidosis, restoration of adequate circulating volume and reversal of profound acidosis (to pH >7.10) are needed for maximal pressor effect. The potential utility of sodium bicarbonate should be kept in mind during prolonged resuscitation efforts. As already noted, glucocorticoid deficiency also blunts the impact of vasomotor agents. Moreover, vasopressors may be ineffective when serum concentrations of K⁺, Mg²⁺, or ionized Ca²⁺ are strikingly abnormal.

Making optimal choices among vasopressor and inotropic drugs requires a clear understanding of the operative pathophysiology, an understanding of adrenergic receptor distribution and action, and a working knowledge of the pharmacologic alternatives. The vasopressor and inotropic drugs are classified by their tendencies to stimulate receptors with different physiologic actions (Fig. 3-3). Alpha effects are vasoconstricting in the peripheral circulation. β1 receptor activation is both chronotropic and inotropic. β2 effects induce vasodilation and bronchodilation (Table 3-2). Dopaminergic (Δ) receptor activation increases renal blood flow, but these Δ effects are usually overwhelmed by the simultaneous α and β actions of the drugs available to elicit them. The ability to select the appropriate agent requires not only the knowledge of the drug's properties but also an assessment of the action required. For example, a tachycardic and hypotensive patient with warm extremities may respond best to a nearly pure α stimulator, such as phenylephrine, whereas a hypotensive patient who has cold, clammy extremities may respond better to dobutamine, a potent inotropic agent with modest vasodilating action and less tendency for chronotropic stimulation than dopamine. For any given patient, optimal therapy may involve several
vasoactive agents with complementary actions. It is worth considering, however, that certain drugs—notably dopamine—can stimulate either \( \beta_1 \) or \( \alpha \) adrenergic receptors preferentially, depending on dosage. Moreover, the sensitivity to any specific dosage varies widely among patients. For a volume-replete but hypotensive patient, the problem is either inadequate pump function or insufficient vascular tone. As a principle, it is desirable to titrate a single well-selected drug to effect (or toxicity) before it is abandoned or supplemented by additional agents. Whatever drug or drug combination is selected, its physiologic impact must be monitored appropriately (see Chapter 2). The ongoing need for these potent and potentially hazardous agents, as well as their dosage, must be reassessed frequently. Over time, patients tend to become “dependent” on these agents, so weaning rather than abrupt termination generally is the most prudent course.

**Adrenergic Receptors and Associated Responses**

<table>
<thead>
<tr>
<th>Alpha Receptors</th>
<th>Beta-1 Receptors</th>
<th>Beta-2 Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoconstriction</td>
<td>Cardioacceleration</td>
<td>Vasodilatation</td>
</tr>
<tr>
<td>Pupil dilatation</td>
<td>Increased cardiac contractility</td>
<td>Bronchodilatation</td>
</tr>
<tr>
<td>Piloerection</td>
<td>Lipolysis</td>
<td>Increased glycolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uterine relaxation</td>
</tr>
</tbody>
</table>

**FIGURE 3-3.** Adrenergic receptor categories and their associated physiologic actions.

**Table 3-2. Inotropic Drugs**

<table>
<thead>
<tr>
<th>Adrenergic Receptor Activation</th>
<th>Relative Effects in Midrange of Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inotropic</td>
</tr>
<tr>
<td>Milrinone</td>
<td>0</td>
</tr>
<tr>
<td>Dobutamine ( \alpha \beta 1 \beta 2 )</td>
<td>+++</td>
</tr>
<tr>
<td>Dopamine ( \alpha \beta 1 \Delta )</td>
<td>+++</td>
</tr>
<tr>
<td>Epinephrine ( \alpha \beta 1 \beta 2 )</td>
<td>+++</td>
</tr>
<tr>
<td>Isoproterenol ( \beta 1 \beta 2 )</td>
<td>++++</td>
</tr>
<tr>
<td>Methoxamine ( \alpha )</td>
<td>0</td>
</tr>
<tr>
<td>Norepinephrine ( \alpha \beta 1 )</td>
<td>+++</td>
</tr>
</tbody>
</table>
Phenylephrine \( \alpha \beta \)
\[ + \quad 0 \quad +++^a \]

Vasopressin
\[ 0 \quad + \text{ or } - \quad + \text{ or } - \quad + \text{ to } +++ \]

Levosimendan
\[ 0 \quad ++ \quad + \text{ or } - \quad 0 \text{ to } - \]

\(^a\)Effect dependent on dosage range.

**Specific Agents**

Potent vasoconstrictors (e.g., epinephrine, norepinephrine, phenylephrine, and dopamine) are best administered through a central line to avoid tissue necrosis resulting from extravasation.

**Catecholamine Receptor Stimulators**

**EPINEPHRINE**

Epinephrine has balanced \( \alpha \) and \( \beta \) agonist properties and serves as the nonselective and potent standard to which all other vasopressors are compared. Epinephrine “coarsens” ventricular fibrillation and augments arterial tone during cardiac arrest. MAP, systemic vascular resistance (SVR), and CO are boosted in patients with an organized heart rhythm. Although epinephrine may prove effective when other vasoactive drugs fail (e.g., in anaphylactic shock), potential side effects include palpitations, arrhythmias, and angina caused by increased myocardial oxygen consumption. Concern has also been raised that epinephrine may interfere with mitochondrial function and contribute to splanchnic ischemia (concurrent administration of dobutamine may attenuate the latter). For patients with hypotension caused by ischemia-induced pump dysfunction, epinephrine may increase myocardial oxygen delivery to a greater degree than it increases myocardial oxygen consumption. Patients already taking \( \beta \)-blocking drugs may experience unopposed \( \alpha \) effects when given a balanced \( \alpha \) and \( \beta \) agonist such as epinephrine.

**NOREPINEPHRINE**

Norepinephrine (levarterenol) combines intense \( \alpha \) with moderate \( \beta_1 \) activities. Its primary effect, therefore, is to vasoconstrict. Despite increases in SVR and LV afterload, CO usually remains stable or improves because of offsetting augmentation of HR and contractility. However, excessive increases in afterload induced by norepinephrine may reduce CO. Side effects include hypertension and increased myocardial oxygen consumption. Norepinephrine is often useful in the early phases of septic shock, a condition in which CO is normal or elevated but SVR is reduced. Although the usual dosing range (0.5 to 20 \( \mu \)g/min) is generally effective, patients with refractory shock may require doses 10-fold higher to show adequate BP response. Such high doses do not appear to be associated with worsened side effects, but from present evidence, it is not clear whether they improve outcome. Norepinephrine frequently is combined with dobutamine, vasopressin, or other complementary pressor agents (such as milrinone) in the setting of refractory shock.

**ISOPROTERENOL**

Isoproterenol has primarily \( \beta_1 \) (chronotropic and inotropic) actions but also possesses the \( \beta_2 \) properties of vasodilation and bronchodilation. Although now used only rarely, it will increase HR and CO in the setting of marked bradycardia (e.g., 3-degree atrioventricular [AV] block). Although now supplanted by effective antiarrhythmics, isoproterenol was formerly used to increase HR and shorten the QT interval in patients with arrhythmias resulting from QT prolongation (e.g., torsades de pointes). Increases in CO because of isoproterenol result primarily from increases in HR. MAP may actually fall, despite rising CO, as a result of
peripheral vasodilation.

**NEO-SYNEPHRINE**

Neo-Synephrine (phenylephrine) is a pure α agonist that lacks cardiac stimulant properties. In high doses, increases in afterload resulting from neosynephrine may actually decrease CO. Neo-Symphrine is used to increase BP in the treatment of supraventricular tachycardias and currently sees some use in combination with intravenous nitroglycerin in patients with acute cardiac ischemia. Used together in that setting, they provide decreased preload and coronary vasodilation while maintaining arterial BP.

**DOPAMINE**

Dopamine is a naturally occurring precursor of norepinephrine with a spectrum of effects that varies with the infusion rate, clinical pathophysiology, and individual responsiveness. In normal subjects, very low infusion rates (1 to 2 μg/kg/min) theoretically improve renal blood flow, but the weight of current evidence indicates that any such effect is insignificant in the critically ill. At doses of 2 to 5 μg/kg/min, dopamine has primarily β1 actions and very mild β2 effects. At such doses, dopamine independently stimulates renal dopamine receptors, increasing renal blood flow, enhancing glomerular filtration rate (GFR), and promoting Na+ excretion. Although the dopaminergic effects are not lost, α effects become more prominent at doses between 8 and 12 μg/kg/min. In still higher doses, dopamine possesses a pharmacologic profile much like that of norepinephrine. Dopamine increases the potential for tachycardia and arrhythmias, having a greater tendency for this unwanted side effect than dobutamine. High doses cause intense vasoconstriction and, if extravasated, may induce soft tissue necrosis—an effect antagonized by local infiltration of phentolamine.

**DOBUTAMINE**

Dobutamine is an isoproterenol analog with primarily β1 actions. Dobutamine causes much less α stimulation than does dopamine and less β2 activity than does isoproterenol. Unlike isoproterenol, dobutamine boosts CO primarily by increasing SV rather than HR. Dobutamine is best suited to the treatment of low CO states in patients with a near-normal BP and good peripheral vascular tone. It is often given together with norepinephrine or phenylephrine, which helps offset its peripheral vasodilating effects. At commonly used doses, dobutamine is less likely than isoproterenol or dopamine to produce tachycardia, but mild increases in HR occur frequently, particularly in hypovolemic patients. Rarely, dobutamine increases AV conduction in patients with atrial fibrillation or flutter, leading to accelerated HR. In some patients with a very high baseline SVR, dobutamine may cause sufficient peripheral vasodilation to induce hypotension.

**Noncatecholamine-Based Agents**

**AMRINONE AND MILRINONE**

Amrinone and milrinone are phosphodiesterase inhibitors with inotropic and vasodilating properties similar to dobutamine, but with even less tendency to cause arrhythmias. These agents have inotropic properties distinct from the catecholamines or digitalis glycosides. Amrinone is a positive inotrope and vasodilator that raises CO by increasing SV, not by increasing HR. Although useful in treating refractory heart failure, vasodilation not offset by a simultaneous α stimulator may give rise to limiting hypotension. While renal excretion provides the primary route of clearance, hepatic metabolism is significant. Therefore, the drug may accumulate in patients with either hepatic or renal failure. Increases in inotropic activity may aggravate outflow obstruction in hypertrophic cardiomyopathy. Increased ventricular rates have been reported during atrial fibrillation or flutter, but the chronotropic effect is generally less than that with any other currently available inotrope. Thrombocytopenia occurs in a small minority of patients. High doses of amrinone given for long periods of time may elevate liver function tests or cause frank hepatic necrosis.
VASOPRESSIN

Vasopressin, a relatively weak vasoconstrictor at concentrations encountered in healthy normal subjects, has several applications in modern critical care practice. For many years this drug has been known to reduce portal pressures and has been used for that purpose in upper GI hemorrhage due to gastric and esophageal varices. More recently, low-dose vasopressin has been shown to have additive effects when combined with a catecholamine-based vasoconstrictor (e.g., norepinephrine), particularly in the setting of refractory septic shock. Although not dramatically effective when used independently, vasopressin tends to boost urine output and improve other signs of shock when used as a secondary (supplemental) agent. Clinical trials suggest that its use be directed toward those in whom the catecholamine-based agents are insufficient to sustain an adequate perfusing pressure. Vasopressin should be considered a complement to—not replacement for—catechol vasopressors. In the setting of cardiopulmonary arrest secondary to ventricular fibrillation or pulseless ventricular tachycardia, the use of vasopressin as an alternative or complementary vasoconstrictor to epinephrine has gained traction in current practice.

GLUCOCORTICOIDS

The hypotensive consequences of acute adrenal crisis have been known for the better part of a century. Only recently, however, has relative adrenal insufficiency (glucocorticoid levels inappropriate to severe stress) been recognized to complicate the course of critical illness, especially in patients with debilitating underlying diseases. Replacement of glucocorticoids may be crucial to reversing shock physiology in such patients. Unless extremely high or extremely low, a single measured cortisol level is not adequate to assess competence or reserve. Although a matter of some controversy, many experienced intensivists consider response to an adrenocorticotropic hormone (ACTH) analog (cosyntropin) necessary to justify its ongoing use. There also is general agreement that many patients in shock who remain hypotensive after fluid repletion and vasopressors will respond to “stress dose” glucocorticoids (preferably 200 to 300 mg of hydrocortisone, given in 3 or 4 divided doses per day over 3 to 7 days). Rapidity of resuscitation in response to steroids is supported by the results of large, recent clinical trials, whereas the impact on mortality has yet to be convincingly shown. Mineralocorticoid supplementation is not essential to the response, but is sometimes given as well. Because hydrocortisone acts relatively quickly and has such a high therapeutic index of benefit to risk, it seems reasonable to embark on such a regimen in virtually any patient with refractory shock, independently of the stimulation test results.

GLUCAGON AND INSULIN

The primary application of glucagon, which inhibits phosphodiesterase and improves myofibrillar calcium availability, is in the treatment of β-blocker overdose. These patients may be desperately ill and in shock because of the negative inotropic and chronotropic effects of those agents. Atropine and isoproterenol are often helpful, but when ineffective or contraindicated, glucagon 0.5 to 5 mg initial bolus followed by a continuous infusion of 1 to 5 mg/h may be indicated. Glucose, insulin, and potassium solutions have been used for many years in diverse settings and with variable results. Very recently, high-dose insulin (1 to 10 units/kg/h and with very closely monitored glucose and potassium blood concentrations) has been gaining strong support from animal and clinical experiments as a preferred therapy over glucagon or milrinone for overdoses of β-blocker, calcium channel blocker, or mixed ingestions with cardiotoxic properties arising from adrenergic, calcium and/or sodium channel blockade. (Tricyclic antidepressants and bupivacaine are examples of the latter.)

OTHER DRUGS
In specific settings—for example, acute hyperkalemia and calcium channel blockade—calcium chloride may be invaluable. Furthermore, although not routinely indicated, it should be kept in mind that severe acidosis may limit catecholamine effectiveness; cautious administration of bicarbonate or alternative buffer (such as tromethamine [THAM]) may effectively serve as a complementary vasopressor. (Raising pH is particularly effective in hyperkalemia.) Levosimendan, a calcium-sensitizing agent now in clinical trials, has shown promise as a cardiac contraction-improving agent that may be superior to phosphodiesterase inhibitors (milrinone-like drugs) in the setting of cardiogenic shock. Finally, afterload-reducing agents (lisinopril or even nitroprusside) may sufficiently improve the ejection of a failing LV to improve perfusion of vital organs without compromising BP.

**A General Strategy for Managing Hemodynamic Instability**

Faced with managing a hypotensive patient with suspected hypoperfusion due to insufficient cardiac priming or impaired vascular tone, it is important to have a consistent and logical approach to choosing interventions. Three important questions must be answered: (1) Is pump performance impaired because of structural or functional causes (e.g., myocardial infarction or ischemia, arrhythmia)? (2) Is the problem one of insufficient preloading? (3) Is vasomotor tone impaired? These questions usually need to be answered by functional testing—a therapeutic challenge to each physiologic component, approached in a defined sequence that begins with a test of preload adequacy and proceeds to pharmacologic interventions aimed at the vessels and heart, depending on response. One rational schema for managing hypoperfusion by fluid and drug therapy is presented in Figure 3-4. In the most challenging cases, these basic and commonplace measures prove insufficient and may benefit from rescue and temporary support by mechanical interventions.

**Mechanical Interventions and Devices**

The output of the failing LV is sensitive to reductions in afterload (the fiber tension developed during systole) and relatively insensitive to reductions in precontractile fiber stretch or preload. Reducing the vigor of respiratory efforts may partially relieve the burden of the failing heart simply by decreasing its output requirements. Moreover, conversion to positive-pressure-assisted breathing raises the mean intrathoracic pressure, reducing the afterload to the LV without compromising its effective preload. For similar reasons, the application of PEEP can be an extremely helpful intervention in this setting.

Pacemakers can boost CO and reduce left atrial filling pressure when used on patients whose HR is inappropriately low relative to VO₂. AV sequential pacemakers are perhaps most physiologic, but their insertion requires special skills not commonly available in the ICU setting. Pacemakers are discussed in greater detail in Chapter 4.

Fluids and vasoactive agents traditionally have been the primary options for support of failing circulation but, recently, mechanical devices have been developed and used on occasion for special indications. Once stabilized, left ventricular assist devices (LVAD) can provide temporary support options for patients with myocardial failure (Fig. 3-5). Problems of infection, immobility, embolism, and cost have limited the use of implantable devices. Much more experience has accumulated with the IABP (Fig. 3-6). This device is inserted in a retrograde fashion through the femoral artery into the descending aorta, above the renal arteries. Cycle-by-cycle diastolic inflation of the large tube-shaped aortic balloon augments both coronary artery and systemic perfusion pressures. Balloon deflation during systole reduces LV afterload, improving systemic perfusion. Ischemia of renal and peripheral arteries, cholesterol or gas embolism, stroke, coagulopathy,
hemolysis, infection, and aortic dissection constitute major hazards. The IABP has been proven to be most useful in temporary support of patients with acute mitral insufficiency, ventricular septal defects, postsurgical and post-angiostent-related “stunning,” or myocardial ischemia refractory to medical therapy (see Chapter 21). Gradual weaning from IABP usually is required and generally accomplished by reducing the ratio of balloon-assisted to unaided cardiac cycles. The IABP may be life sustaining for patients awaiting cardiac transplantation. For patients without appropriate physiology (aortic insufficiency, mitral stenosis, aortic dissection) or correctable mechanical defects, IABP and other ventricular assist devices are of unproven benefit and/or contraindicated.

**FIGURE 3-4. Decisions in resuscitation from hypotension.** If these remedies prove inadequate to augment perfusion, other measures may be considered such as reducing cardiac demand and varied forms of rhythm management or mechanical assistance.
FIGURE 3-5. Catheter-inserted left ventricular assist device. The axial pump within the catheter can offload the ventricle by as much as 2 L/min forward flow.

FIGURE 3-6. Mechanical events and arterial pressure tracing during one cardiac cycle aided by the intra-aortic balloon pump.
Over the past decade there has been increasing enthusiasm for extracorporeal gas exchange (ECMO), a technology that is rapidly becoming safer and more effective. The ability to augment oxygen exchange and CO₂ removal when the lungs become inefficient (e.g., ARDS) reduces overall demands from the tissues for both the heart and lungs. Venovenous circuits require extracorporeal diversion of blood flow which may stress the tolerance of the patient newly resuscitated from shock. Venoarterial ECMO, however, is often a suitable choice for such marginal patients in that it can help to support hemodynamics as well as complement pulmonary gas exchange (Fig. 3-7).

CONGESTIVE LEFT HEART FAILURE
The basic physiology underlying management of CHF is detailed in Chapter 1. In essence, the shared problem of left-sided conditions relates to an imbalance between the hydrostatic pressure in the fluid-exchanging vessels of the lung (capillaries, small arterioles, and small venules) on one hand and the vascular oncotic forces and the pulmonary lymphatic drainage capacity on the other. Because neither lymphatic drainage nor vascular oncotic pressure can be improved easily or rapidly, clinical attention usually centers on reducing the left atrial pressure that regulates the filtering pressures upstream. Isolated right heart failure (cor pulmonale) and right ventricular infarction are discussed in Chapters 1 and 21, respectively.

Causes
Left atrial pressure can rise for many reasons: reduced compliance of the left heart secondary to hypertrophy, ischemia, catecholamines, or interdependence with a swollen right ventricle (see diastolic dysfunction, discussed previously); impaired contractility because of intrinsic myocardial disease, circulating depressant factors, or performance-impairing drugs; pathologically slow or inappropriately rapid HRs (requiring higher filling pressure to support SV or preventing adequate filling of the LV, respectively); conduction system disease and arrhythmias; or valvular stenosis or insufficiency of the mitral or aortic valves. Pulmonary congestion may be accompanied by adequate or insufficient forward output, depending on underlying cardiopathy and precipitating cause for the exacerbation.
FIGURE 3-7. Venoarterial extracorporeal membrane oxygenation. Pump-driven catheter flow assists the heart in building aortic pressure and improving perfusion adequacy.

Precipitants
For a predisposed patient, decompensation usually is brought on by excessive demands for CO relative to capacity to meet them (fever, increased work of breathing, physiologic stress); medication error or noncompliance; an adverse change in cardiac preload (renal insufficiency, overly zealous administration of intravascular volume, dietary indiscretion); a sudden augmentation of cardiac afterload (hypertension, ischemia, forceful inspiratory efforts); or alterations in myocardial compliance, heart rhythm, or contractility (electrolyte disturbances, ischemia, and sepsis are major offenders in this latter category).

Diagnosis
The key bedside indicators of pulmonary congestion are well known—new crackles, wheezes, and rhonchi; the appearance of an S₃ gallop; and, in many instances, distended neck veins, cool extremities, diaphoresis, and tachypnea. Alert patients almost always—but not invariably—experience exertional dyspnea and orthopnea. Hyponatremia and an elevated BUN/Cr ratio reflect prerenal perfusion inadequacy. Atrial and brain natriuretic peptides (ANP and BNP) are released in response to high ventricular filling pressures—whether induced by systolic or diastolic dysfunction. These peptides exert natriuretic, diuretic, and hypotensive effects (in part mediated through inhibition of the renin-angiotensin system) that may prove useful in both diagnosis and therapy (see following). BNP is more sensitive to aberrations of ventricular function and, therefore, is both more useful and widely used than is ANP. Values of BNP less than 100
pg/mL argue strongly against heart failure or volume overload as the primary cause of dyspnea, whereas values that exceed 400 pg/mL are highly suggestive—but not diagnostic—of contributions from those causes. Intermediate values suggest chronic LV dysfunction or cor pulmonale. Clearly, more than one reason for dyspnea may be present, so an elevated BNP level does not necessarily establish congestive failure as the primary cause. Although BNP can be released in other conditions and is affected by renal dysfunction and attenuated by obesity, BNP serves as a useful monitor of CHF treatment effectiveness in the outpatient setting and has prognostic value in the setting of acute coronary syndrome. Interestingly, BNP levels may be helpful in gauging the adequacy of dialysis for intravascular volume regulation.

The chest radiograph often exhibits characteristic features: Kerley lines, blurred hilar structures, pleural effusions, a widened vascular pedicle, and diffuse, symmetrical infiltrates with relatively spared costophrenic angles and without prominent air bronchograms. A balloon occlusion wedge pressure confirms an elevated pulmonary venous pressure that rises sharply after volume challenge. The echocardiogram usually provides evidence of a dilated left atrium, distended vena cava, impaired contractility, or diastolic dysfunction (see Chapter 2).

Management of Congestive Failure

The sitting position, supplemental oxygen, diuresis, afterload reduction, adequate sedation, and relief of an excessive breathing workload by continuous positive airway pressure (CPAP), biphasic airway pressure (Bi-PAP), or invasive mechanical ventilation are fundamental to the care of patients with acute left heart failure. Opiates and nitrates may also be useful in acute pulmonary edema (see below). In general, the intravenous route is preferred for essential medications because those given orally may be sluggishly absorbed by the stressed, underperfused, and edematous bowel mucosa.

Diuresis not only reduces excessive left atrial pressure but also acts to reduce right ventricular overdistention, relieve myocardial wall tension, and lessen afterload. For fragile patients and those responding slowly to bolus dosing of loop diuretics, consideration should be given to the use of a furosemide or bumetanide drip to more closely observe and consistently regulate diuresis (rather than repeated boluses). The addition of an intravenous thiazide (e.g., chlorothiazide) may amplify the effect of the loop diuretics. Venous ultrafiltration can be extremely effective and well tolerated for removing fluid in patients without adequate urinary response to diuresis. These pump-driven circuits can remove up to 200 mL/fluid/h. For those with hypoproteinemia, the simultaneous administration of albumin not only increases intravascular volume and oncotic pressure but also improves delivery of these loop diuretics to their primary site of action. Nesiritide may prove an effective (but expensive) agent in well-selected patients who are not effectively managed by diuretics and salt restriction, but is not appropriate for routine use (see following).

Precipitating causes must be identified and eliminated, if possible. Patients with limited cardiac reserve are especially vulnerable to new-onset arrhythmias. Electrical cardioversion of rapid atrial arrhythmias and slowing of rapid atrial fibrillation with diltiazem, amiodarone, esmolol, metoprolol, or digoxin may sometimes be indicated. Although vasodilating agents should always be used with caution, opiates (morphine, fentanyl) and nitrates have multiple therapeutic effects in carefully selected patients with adequate BP. Morphine and its analogs relieve anxiety, thereby reducing O₂ consumption, and morphine also doubles as a venodilator that reduces central vascular volume. For its pharmacologic properties, fentanyl is often used when repeated or continuously regulated opiate effects are required, especially in patients with renal insufficiency. (Its carrier volumes, however, may simultaneously deliver an unwanted fluid load.) Nitrates also increase venous capacitance, simultaneously
dilating the coronary vasculature in patients with ischemic disease. Although short-acting β-blockers may clearly be helpful in treating patients with adequate systolic function and appropriate indications (e.g., rapid arrhythmia, ongoing ischemia, thyrotoxicosis), extreme caution should attend their use in other acute settings of decompensated heart failure. Both β-blockers and ACE inhibitor/receptor antagonists are valued for long-term treatment of CHF, but it is not advisable to begin either until the acute exacerbation is resolving and BP is well restored. Those already receiving these agents should be managed as indicated above.

**Vasoactive Drugs in Hypertensive CHF**

Nitroprusside and hydralazine can be helpful when CHF is either caused or exacerbated by systemic hypertension. Angiotensin-converting enzyme (ACE) inhibitors reduce the ejection impedance of the afterload-sensitive LV and often prove fundamental to successful management. Although calcium channel blocking agents can also be used for this purpose, they also tend to suppress ventricular contractility.

Verapamil is the greatest offender in this regard; nifedipine and nimodipine are better tolerated.

**Cardiotonic Agents in CHF**

Digoxin has served a time-honored but increasingly limited role in improving the contractility of a dilated heart. In the critical care unit, many practitioners reserve it for controlling HR in atrial fibrillation when the need is not immediate and alternative rate controllers are less desirable because of their potential for adverse inotropic effects. As in treatment of overt shock, catecholamine-based inotropes such as dobutamine or dopamine are generally the agents of choice, unless their tendency to increase HR overcomes the inotropic benefit by reducing LV filling time or by inciting ischemia. Milrinone may be particularly useful in circumstances in which inotropy is desired but concomitant elevation of HR must be minimized. Occasionally, norepinephrine or phenylephrine helps to maintain coronary perfusion pressure and sustain forward output when hypotension accompanies failure. For patients with florid pulmonary edema, intubation and mechanical ventilation may be a key therapeutic intervention if CPAP and noninvasive ventilation by mask is not feasible or is poorly tolerated, acidosis is progressing, or hypoxemia and the work of breathing are severe.
FIGURE 3-8. Treatment algorithm for varied stages of congestive heart failure.

**Nesiritide**

Although clearly not appropriate for routine use, nesiritide, a recombinant analog of human BNP that is given by intravenous infusion, may be an effective agent in the treatment of severe heart failure. The mechanism of action is debated, but it seems likely that it counterbalances vasoconstricting and antidiuretic neurohormones as well as promotes natriuresis. Nesiritide is worth considering when BP is adequate, the circulation is full, intravenous diuretic therapy is relatively ineffective, and/or moderate renal dysfunction complicates severe CHF (without shock). Although nesiritide can be used for many days and then abruptly discontinued, its effects tend to persist for several days after the CHF exacerbation has resolved. The N-terminal fragment of the prohormone from which endogenous BNP is cleaved (N-pro-BNP) serves as an effective monitor of its activity (see Chapter 2).

**Transition from Acute to Chronic Phase of CHF**

The process of acute phase stabilization merges into the supportive cares needed for recovery and longer term maintenance of persisting cardiac insufficiency. In the various stages of CHF, different combinations of drugs, activity modification, pacing, resynchronization therapy, and surgical intervention may be warranted (Fig. 3-8).

**SUGGESTED READINGS**


Chapter 4

Arrhythmias, Pacing, and Cardioversion

• Key Points

1. Many arrhythmias require drug treatment; however, those that are asymptomatic, chronic, and stable, are related to a temporary physiological disturbance (e.g., transient hypoxemia, electrolyte abnormalities) can be observed while the underlying problems are corrected.

2. Correction of hypoxemia and electrolyte disturbances is essential to minimize the risk of arrhythmias and to facilitate conversion to a stable baseline rhythm.

3. Patients with marginally compensated hemodynamics, impaired diastolic compliance and/or limited systolic reserve are particularly vulnerable to new-onset arrhythmias.

4. Symptomatic patients with tachyarrhythmias of uncertain origin should usually be treated as if they have ventricular arrhythmias, regardless of QRS complex width, especially if hypotensive.

5. Narrow complex tachycardias can be diagnosed or terminated in many cases by using carotid sinus massage and intravenous adenosine.

6. A large proportion of patients treated with antiarrhythmics will develop side effects, which may include new or worsened arrhythmias.

7. Temporary pacemakers are indicated for (1) high-grade (especially symptomatic) atrioventricular block following myocardial infarction, (2) overdrive suppression of refractory atrial tachyarrhythmias, (3) suppression of torsades de pointes emerging from bradycardia, (4) sick sinus syndrome, and (5) control of post-cardiac surgery arrhythmias.

8. Standby pacing capability should be available during high-risk cardioversions and during right heart catheterization in patients with underlying conduction system disease (e.g., left bundle branch block).

The treatment of arrhythmias has become somewhat simpler and more effective in response to a series of discoveries and technologic developments. For example, it has been learned that many patients with atrial fibrillation (A-fib) do not need conversion to sinus rhythm and that the suppression of premature ventricular contractions (PVCs) does not invariably improve outcomes. The sophistication, safety, and effectiveness of drug therapy and implantable and transthoracic pacing systems have clearly improved. Radiofrequency ablation now makes many chronically troublesome arrhythmias curable, and for arrhythmias that cannot be cured, (e.g., genetic long QT syndrome, recurrent sudden death, dilated cardiomyopathy), implantable defibrillators have been lifesaving. Adenosine has been immensely helpful for diagnosis and therapy, and the role of amiodarone in treatment was redefined. Finally, the widespread application of rapid reperfusion strategies for acute coronary syndrome has reduced or eliminated many peri-infarction arrhythmias and prevented many that previously arose from postinfarction heart failure. Despite these advances, the critical care physician must still be able to make an accurate diagnosis of an arrhythmia by rapidly interpreting an electrocardiogram (ECG) (Fig. 4-1) and providing appropriate emergency treatment when indicated.

COMPONENTS OF THE ELECTROCARDIOGRAM

The first step in evaluation of the ECG is to identify atrial activity (P waves), which is best seen in the inferior leads (II, III, and aVF). P wave shape should be examined for beat-to-beat uniformity; the pattern should be
of the P wave relative to the QRS complex. P-wave inversion in limb lead II signifies the retrograde atrial depolarization diagnostic of a nonsinus mechanism. After the atrial rhythm has been characterized, ventricular activity (QRS complex) should be inspected. If the QRS is narrow, ventricular depolarization most likely occurs in response to normal atrioventricular (AV) conduction or at least is of supraventricular origin. A QRS complex (>0.12 second) suggests (1) ventricular origin; (2) an aberrantly conducted supraventricular beat, such as a left or right bundle branch block (Fig. 4-2); (3) a bypass pathway; or (4) supraventricular conduction delayed by a drug (e.g., tricyclic antidepressant) or electrolyte (e.g., hyperkalemia) abnormality. The QRS should be evaluated for regularity, rate, and the relationship to the P waves. If every QRS complex is not preceded by a P wave, some form of AV block, or A-fib or flutter, or ventricular tachycardia (VT), is likely. Because of the normal delays associated with AV nodal conduction, a QRS complex occurring less than 0.1 second after a P wave is unlikely to be related to it.

![Diagram of ECG complex with annotations](image)

**FIGURE 4-1.** Key diagnostic features of the ECG complex used in electrophysiologic analysis. The rate-corrected QT interval (QTC) is QTC = QT/√(RR).

**GENERAL APPROACH TO ARRHYTHMIAS**

Acute arrhythmias are detrimental when they are symptomatic, reduce tissue perfusion, or increase myocardial oxygen demand. Protracted tachyarrhythmias themselves can impair myocardial function. In making management decisions, the patient's symptoms, adequacy of perfusion, risks of treatment versus observation, and chronicity of the problem must all be considered. Tachyarrhythmias evoking unconsciousness, hypotension, pulmonary edema, or angina should be terminated immediately, as should symptomatic bradycardia. Patients with isolated PVCs lacking evidence of heart failure or ischemia have an excellent prognosis without treatment. In such
patients, drug suppression of the arrhythmia is unlikely to improve outcome, but is apt to produce untoward side
effects. A past history of well-tolerated arrhythmia similar to the one currently present also suggests that rapid
treatment is not necessary. Conversely, patients with myocardial ischemia and those with a history of malignant or
degenerative arrhythmias should be treated aggressively. Arrhythmias are often provoked or exacerbated by
electrolyte disturbances, mechanical irritation of the heart, drugs, and ischemia. Thus, hypokalemia or
hyperkalemia, hypomagnesemia, alkalosis, anemia, and hypoxemia all aggravate arrhythmic tendencies.
Intracardiac catheters, pacemaker malfunction, digitalis, theophylline, and sympathomimetic agents (e.g.,
catecholamines, cocaine) can provoke a wide variety of arrhythmias that cease upon their removal. It is also
clear that several antiarrhythmic drugs (e.g., quinidine, sotalol, flecainide) can have serious proarrhythmic
effects. Electrical instability is also heightened by ischemia. For example, hypotension reduces myocardial
perfusion, whereas excess intravascular volume or high ventricular afterload can increase wall tension, afterload,
and oxygen demand.

FIGURE 4-2. Distinguishing ECG features of left and right bundle branch blocks.

Dealing with Uncertainty
Minimally symptomatic narrow complex tachyarrhythmias and pulseless arrhythmias seldom present diagnostic or
therapeutic dilemmas. By contrast, an unfamiliar arrhythmia, especially a wide complex tachycardia (WCT)
occurring in a patient with a moderate decrease in blood pressure or modest symptoms, is often anxiety
provoking. The first step when confronted with an unfamiliar arrhythmia is to confirm that it is real. Electrical artifacts may occur as a result of poor surface electrode contact or electromechanical devices such as aortic balloon or infusion pumps. Shivering, seizure activity, and tremors of Parkinson disease can produce ECG artifacts that may be confused with serious arrhythmias.

The most consternation is caused by monomorphic WCT not clearly of ventricular or supraventricular origin. To avoid mistakes under pressure, it is important to develop an approach to diagnosis and therapy in advance (Table 4-1). When patients are hemodynamically compromised, it is best to treat arrhythmias as if they were life threatening, as the majority of WCTs have a ventricular origin. In such circumstances, the best course of action is immediate cardioversion. However, when the rhythm is hemodynamically well tolerated and dyspnea is very mild or inapparent, it is important to exclude the presence of high-grade AV block; infranodal escape rhythms must not be terminated before treating the underlying heart block. Hence, patients with symptomatic WCT should receive either cardioversion or drug therapy for VT (e.g., amiodarone, lidocaine, procainamide), depending on clinical urgency. Traditionally, lidocaine has been the drug of first choice, and failure to respond to it does support a diagnosis of supraventricular tachycardia (SVT) with aberrant conduction. However, in this setting, procainamide and amiodarone are also good choices because they will control many types of SVT and VT. Although these drugs rarely help clarify the diagnosis, they often control the rhythm long enough to get expert advice or perform more sophisticated diagnostic maneuvers. In the patient failing a trial of lidocaine, adenosine may also be tried. By transiently blocking the AV node, adenosine is very effective at slowing or terminating SVT. Adenosine is not a good choice, however, if the patient is known or suspected to have a bypass tract. In cases of WCT, verapamil or diltiazem is a suboptimal choice for empirical therapy because their cardiodepressant and vasodilating properties often lower the blood pressure, and SVTs utilizing a bypass tract can be accelerated. A discussion of the most common arrhythmias and their treatment follows.

Table 4-1. Treatment for Regular Monomorphic Wide Complex Tachycardia of Uncertain Origin

<table>
<thead>
<tr>
<th>Pulseless or symptomatic hypotensive patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate unsynchronized cardioversion.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>For less urgent circumstances (minimal symptoms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine (1-1.5 mg/kg bolus)</td>
</tr>
</tbody>
</table>

↓

<table>
<thead>
<tr>
<th>Amiodarone (150 mg @ 15 mg/min)</th>
</tr>
</thead>
</table>

May repeat × 2-3 at 10 min intervals if rhythm not reversed

↓

| Consider DC synchronized cardioversion if drug treatment fails |
TACHYARRHYTHMIAS

Sinus Tachycardia

Sinus tachycardia (ST) is the primary means of raising cardiac output in response to metabolic demands; thus, it is physiologic in the setting of exercise, fever, or hyperthyroidism. ST is also appropriate compensation for hypovolemia, limited stroke volume, reduced systemic vascular resistance, or reduced myocardial compliance. Anxiety, pain, and drugs (e.g., catecholamines, cocaine, theophylline) may also be responsible. Unless ST causes ischemia by increasing myocardial oxygen consumption or precipitates pulmonary edema by shortening diastolic filling time in a patient with reduced ventricular compliance, it is simply a marker of illness. The best therapy for ST is to treat the underlying cause. In patients with symptomatic ischemia, $\beta$-blockade often proves helpful. However, $\beta$-blockers should be used cautiously in tachycardic patients with hypotension, acute infarction, or chronic congestive heart failure because ST often reflects hypovolemia or incipient decompensation. Likewise, caution is indicated using $\beta$-blockers in patients with obstructive lung disease because of the risk of exacerbating bronchospasm.

Nonsinus Supraventricular Tachycardias

The nomenclature surrounding SVT is confusing, but the concepts are simple. SVT usually results from a self-perpetuating reentry mechanism; much less commonly, SVT stems from rapid discharge of an ectopic atrial focus. Graphic examples of the most common forms of SVT are shown in Figure 4-3.

Reentrant Tachycardias Involving the AV Node

Reentrant SVTs occur when two potential transmission pathways have differing conduction speeds and refractory periods, permitting a reverberating circuit to develop. This group of arrhythmias is classified by whether that circuit lies solely within the AV node or whether one limb of the circuit bypasses the AV node. By far the most common form is AV nodal reentrant tachycardia (AVNRT) in which a “micro-reentrant” pathway exists entirely within the AV node. Although sometimes confused with atrial flutter with 2:1 conduction, AVNRT can usually be identified by its isoelectric inter-QRS baseline and slightly irregular, narrow QRS, occurring at a rate 150 to 200 beats/min. QRS complexes frequently exhibit a rate-related, right-bundle branch block pattern that may simulate VT. (P waves are often buried in the QRS complex or T wave, producing a “pseudo-S wave.”) When visible, P waves are frequently inverted in the inferior leads because atrial depolarization characteristically begins in the AV node located low in the right atrium and spreads cephalad. Unlike A-fib or flutter, in which the ventricular response slows to vagal stimulation or adenosine therapy, AVNRT either remains completely unaffected or stops abruptly.
FIGURE 4-3. Stylized electrocardiographic tracings illustrating the distinguishing features of the most common supraventricular arrhythmias. A shows the irregular ventricular response and absence of well-defined P waves characteristic of A-fib. By contrast, B illustrates the rapid inverted “sawtooth” atrial depolarizations of atrial flutter. A 2:1 ventricular response often results in a ventricular rate of 150 beats/min. C shows the most common pattern of AVNRT in which an isoelectric baseline is punctuated by slightly irregular narrow complex ventricular depolarizations. Close examination reveals inverted monomorphic P waves buried in the QRS and T waves. D illustrates the characteristic polymorphic P-wave pattern of MAT.

The less common form of reentrant SVT is AV reentrant tachycardia (AVRT) in which ventricular rates are typically a bit faster (150 to 250 beats/min). AVRT is caused by a “macro-reentrant” circuit in which one conduction limb goes through the AV node and one limb bypasses it. AVRT is subclassified by the direction the current takes through the AV node. If antegrade conduction is through the AV node, it is termed “orthodromic.” Unless there are rate-related conduction delays, in orthodromic AVRT the QRS complex is of normal width because conduction follows the usual AV-node-His-Purkinje pathway. If antegrade conduction occurs through the accessory or bypass tract, the rhythm is termed “antidromic.” Antidromic AVRT may be identified (especially while the patient is in sinus rhythm) by a short PR interval, wider QRS, and delta waves indicative of ventricular preexcitation from the bypass tract. The rare, but best characterized preexcitation condition is Wolff-Parkinson-White syndrome. Antidromic AVRT is important to recognize because such patients are at higher risk of sudden cardiac death, and it may respond paradoxically, sometimes catastrophically, to usual SVT treatments. Intra-SA node, or intra-atrial, reentrant rhythms may also occur but will not be discussed further because of their rarity.

Adenosine and vagal maneuvers like carotid sinus massage are valuable tools to distinguish reentrant SVTs
from VT and from nonnodal-reentrant atrial arrhythmias like A-fib and flutter and ectopic atrial tachycardia. VT is unresponsive to vagal maneuvers, and if the rhythm is A-fib, only transient slowing of the ventricular rate is likely. If the rhythm is flutter, successful block of the AV node will unmask the characteristic flutter waves but will not stop the atrial reentrant circuit.

SVTs are generally well tolerated and self-limited, often requiring no treatment with the possible exception of stopping exacerbating drugs (e.g., theophylline, catecholamines, and cocaine) and correcting electrolyte disorders. If treatment is needed, maneuvers or drugs that inhibit conduction through the AV node are highly effective. Massage of the nondominant carotid artery for 10 to 15 seconds, alone or in conjunction with the Valsalva maneuver, often interrupts AVNRT and AVRT. To avoid cerebral ischemia, both carotid arteries should not be compressed simultaneously, and vessels with bruits and those of patients with a history of stroke or transient ischemia should not be massaged. When mechanical maneuvers fail, drug intervention is indicated. Adenosine has supplanted calcium channel blockers (e.g., verapamil) as the initial therapy of choice for hemodynamically stable SVT. As a potent but short-lived AV node blocker, a 6- to 18-mg IV dose of adenosine terminates AVNRT and AVRT with a success rate equal to or greater than that of verapamil. Although very effective at stopping the original arrhythmia, up to 10% of patients with AVNRT and AVRT convert to A-fib. Though helpful diagnostically, adenosine does not usually terminate A-fib or flutter. Calcium channel blockers, like verapamil, represent second-line therapy but should be avoided when supraventricular origin is in doubt, hypotension is present, or a bypass tract is suspected. The nodal blocking effects may encourage atrial conduction over the bypass tract, and the vasodilating effects of calcium channel blockers may cause hypotension unless rhythm conversion occurs. If used, verapamil doses of 2.5 to 5 mg IV are usually adequate. (Comparable doses of diltiazem may be substituted, but nicardipine is less effective.) β-Blockers like propranolol (0.5 to 1 mg every 5 minute, up to a 4-mg total dose) or metoprolol may also be effective. If the patient's ability to tolerate β-blockade is uncertain, the short-acting esmolol can be tried. Digoxin has long been used in the treatment of AVNRT but often requires hours for full effect, making it most useful in hemodynamically stable patients and in those requiring prophylaxis. By boosting systemic blood pressure, vasoconstrictive drugs (e.g., phenylephrine) may reflexly impede AV-nodal conduction. However, vasopressors may precipitate cardiac or cerebrovascular complications and are therefore usually avoided. Cholinergic stimulants like neostigmine can increase nodal vagal tone, thereby ending nodal reentrant arrhythmias but have an unacceptable side effect profile. Because all of the reentrant circuit resides in the AV node in AVNRT, it tends to be easily broken by AV-nodal blocking measures. Because just one limb of the conducting circuit passes through the AV node in AVRT, adenosine (or any other AV-nodal blocker) often stops the arrhythmia, but there is a risk; blocking antegrade conduction through the AV node may promote rapid conduction through a bypass tract with a very rapid, even life-threatening (VT or VF) response. This complication is most likely in patients who develop A-fib or flutter through a bypass tract after receiving the drug.

Lidocaine has no effect on SVT. Type la antiarrhythmics (e.g., quinidine and procainamide) exert vagolytic effects and often worsen SVT by accelerating AV conduction unless nodal-blocking drugs are administered first. In refractory SVT, temporary overdrive atrial pacing may restore sinus rhythm and is easily accomplished when an atrial pacor pacing pulmonary artery catheter is already in place, as after cardiac surgery. Hemodynamically unstable SVT should be treated with low-energy (10 to 50 WS [watt-seconds]) synchronized cardioversion. An outline of therapy for SVT is presented in Table 4-2.

Table 4-2. Treatment Plan for Narrow Complex Regular Tachycardia
Ectopic Atrial Tachycardia

Ectopic atrial tachycardia can result from a single ectopic (extranodal) focus firing at a rapid rate, or more commonly from multiple rapidly discharging atrial foci. The latter mechanism is known as multifocal atrial tachycardia (MAT) and most often occurs in association with obstructive lung disease or metabolic crisis. However, it also complicates left ventricular failure, coronary artery disease, diabetes, sepsis, and toxicity with digitalis, theophylline, and sympathomimetic drugs. Among patients with lung disease, hypoxemia, hypercapnia, acidosis, alkalosis, pulmonary hypertension, and β-agonist therapy have all been identified as risk factors. When P waves of multiple morphologies are conducted at a normal ventricular rate, the condition is referred to as a “wandering atrial pacemaker.” MAT is recognized by irregularly irregular QRS complexes of supraventricular origin, varying PR intervals, and the presence of at least three morphologically distinct P waveforms on an isoelectric baseline. Comparable heart rates (100 to 180 beats/min) and beat-to-beat variation in PR and RR intervals often cause MAT to be confused with A-fib.

Because ectopic tachycardias do not depend on the AV node for impulse initiation, measures to increase AV-nodal refractoriness are usually ineffective. Although β-blockers, amiodarone, and calcium channel blockers may temporally slow or convert MAT, the definitive treatment is to reverse the underlying cause. Correction of hypokalemia and supplementing magnesium, perhaps even if levels are within the normal range, can be helpful and are unlikely to be harmful unless advanced renal insufficiency is present. (MgSO₄ given as 2 g IV may slow the rate, if not convert the rhythm.) Verapamil (up to 20 mg), or diltiazem, can be useful by decreasing the frequency of the atrial impulses, not by blocking their entry to the ventricle. Unfortunately, verapamil commonly reduces blood pressure, an effect that to some extent can be ameliorated by pretreatment with calcium gluconate. β-Blockade can also control the rate or even abolish MAT, but has obvious limitations for patients compromised by severe lung disease. If β-blockers are used, short-acting agents (i.e., esmolol) or cardioselective blockers (i.e., metoprolol) make the most sense. Metoprolol, 5 mg IV every 10 minute can be tried, and if it is well tolerated, the patient can be converted to an oral dose of 50 to 100 mg once or twice daily. Neither cardioversion, digitalis, nor the antiarrhythmics lidocaine, quinidine, procainamide, and phenytoin benefit patients with MAT. The role of radiofrequency ablation for MAT remains undefined at this time. Whereas theophylline and inhaled β-agonists may occasionally precipitate MAT, their cautious use may improve underlying bronchospasm sufficiently to reverse the arrhythmia. In patients who demonstrate MAT in response to theophylline or β-agonists, corticosteroids or inhaled anticholinergics represent attractive alternative options for treating bronchospasm because they are not cardiostimulatory.
Atrial Fibrillation

A-fib is a common, (prevalence approx. 5% among patients >70 years) chaotic atrial rhythm in which no single ectopic pacemaker captures the entire atrium; hence, there is no distinct P wave on ECG. New onset A-fib often complicates chest surgery, pulmonary embolism, valvular heart disease, obstructive lung disease, and hyperthyroidism. The irregular ventricular rhythm may be confused with MAT, frequent premature atrial contractions, ST, or atrial flutter with variable AV block. Because there is no organized atrial depolarization or contraction to facilitate left ventricular priming, cardiac output may fall significantly at its onset, especially in patients with impaired ventricular compliance. Although the atria may depolarize up to 400 times/min, the AV node rarely conducts impulses at rates higher than 180 to 200 beats/min. However, fever, sepsis, vagolytic drugs, and the presence of accessory conduction pathways may increase the ventricular response. On physical examination, A-fib is suggested by a fluctuating S1 heart sound (because of varying mitral valve position at the onset of ventricular systole) and a pulse deficit (because of occasional systoles with low ejection volumes).

There are three prominent risks of A-fib: hypoperfusion from too rapid a ventricular rate, systemic embolism from clot formation in the noncontractile atrium, and cardiomyopathy from chronic tachycardia.

Treatment is guided by ventricular rate, hemodynamic adequacy, baseline left ventricular function, duration of the rhythm, and presence of a nodal bypass tract. Acute hemodynamic compromise from a rapid ventricular rate (>150) mandates synchronized cardioversion (100 to 200 WS of monophasic energy or the biphasic equivalent). Occasionally, higher energy levels are required. (The longer the duration, the more resistant A-fib is to sustained conversion.) Ventricular rates greater than 200 beats/min suggest accelerated conduction due to vagolytic drugs (e.g., type Ia antiarrhythmics) or presence of an accelerated conduction pathway. If the ventricular rate is less than 60 beats/min, drug effect (e.g., digitalis, β-blockers, calcium channel blockers) or conduction system disease should be suspected. In untreated patients with a slow ventricular response, electrical cardioversion or nodal-blocking drugs may produce symptomatic bradycardia or even asystole—a risk that is sufficiently high in such individuals that a temporary pacemaker should be inserted prior to attempting cardioversion.

There is no rush to correct chronic, hemodynamically stable A-fib. Before conversion is attempted, the likelihood of attaining and maintaining sinus rhythm should be assessed and the risk of systemic embolism must be considered. When left atrial diameter exceeds 4 cm, conversion to stable sinus rhythm is unlikely. Although many clinicians advocate at least one attempt at restoring sinus rhythm, most patients do quite well long term if anticoagulated and the resting ventricular rate is maintained less than 100 beats/min. However, chronic A-fib compromises ability to exercise and/or respond to physical stress. Landmark trials indicate that restoration of sinus rhythm does not result in a significant reduction of the risk of embolization in the well-anticoagulated patient, but in A-fib without anticoagulation the annual risk is substantially higher.

For hemodynamically stable A-fib, the first step in treatment is to slow the resting ventricular rate to ≤100 beats/min. If ventricular function is good, calcium channel or β-blockers are preferred rate-controlling agents. If ventricular function is impaired, digoxin is a better choice, although amiodarone and diltiazem can be used with caution. With digoxin alone or in combination with a β-blocker or calcium channel blocker, approximately 20% of patients with recent-onset A-fib convert to sinus rhythm. Because drugs that block normal AV conduction can accelerate conduction over the bypass tract, calcium channel or β-blocking drugs or digitalis are recommended only if there is reasonable certainty that a nodal bypass tract does not exist. Amiodarone is perhaps the best initial therapy for both rate control and rhythm conversion if a nodal bypass tract is suspected.

If A-fib is of less than 48-hour duration, the ventricular rate is controlled, and it is judged that there is a reasonable likelihood of sustaining sinus rhythm, there are two reasonable courses of action. One is to perform synchronized cardioversion using 100 to 200 WS shock, preferably after balancing fluids and electrolytes and...
ideally after echocardiography to help assure the absence of preformed atrial clot. Cardioversion is highly effective initially, but unfortunately, A-fib recurs in most patients unless pharmacologic inhibition is continued; therefore, it makes little sense to convert patients intolerant of suppressive medications. The alternative course of action is to use amiodarone, ibutilide, or procainamide to chemically convert A-fib to sinus rhythm. Of the available choices, amiodarone is highly effective but has several practical limitations: when given IV, approximately 25% of patients develop hypotension, and chemical phlebitis is not uncommon. Amiodarone has significant β-blocking properties and increases plasma levels of digoxin, both of which can lead to significant bradycardia after rhythm conversion. In addition, amiodarone potentiates the effects of warfarin and routinely results in abnormal thyroid function tests. Though rare, amiodarone can cause pulmonary toxicity, especially when used in high doses or for long periods of time. Procainamide is effective in approximately 40% of patients but is generally poorly tolerated long-term. Ibutilide’s use is limited because the drug is only available parenterally and may rarely act as a proarrhythmic, especially in patients with QT prolongation.

If A-fib has been present for more than 48 hours and reversal is not urgent, anticoagulation should ideally be undertaken for 3 to 4 weeks before rhythm conversion so as to minimize the risk of embolization (unless atrial clot can be excluded with some certainty using transesophageal echocardiography). After conversion, anticoagulation should be continued for another 3 to 4 weeks. For the patient in whom A-fib cannot be corrected, long-term anticoagulation is indicated to prevent systemic embolism and stroke. The annual incidence of stroke averages 1% for patients without mitral valve disease or heart failure but can be as high as 6% for patients with both risk factors.

**Atrial Flutter**

Atrial flutter (flutter) arises in a localized region of reentry outside the AV node or, less commonly, in a rapidly firing ectopic focus. Depolarization usually originates from low in the right atrium, producing inverted P waves in the inferior leads and upright P deflections in lead V1. Flutter frequently complicates pneumonia, exacerbations of chronic lung disease, and the postoperative course of thoracic surgery patients but seldom occurs in association with acute myocardial infarction (MI). Flutter is intrinsically unstable, often converting to A-fib spontaneously or in response to drug therapy. Because the flutter circuit does not involve the AV node, atrial rates are usually quite rapid (260 to 340 beats/min). The AV node cannot conduct impulses at such high rates, so the ventricular response is a fraction, typically ½ or ¼ of the atrial rate. Most commonly, 2:1 AV block leads to a regular ventricular rate of approximately 150 beats/min. The ventricular response can be slowed, but the rhythm is rarely terminated by vagal maneuvers. If there is uncertainty about the rhythm, administration of adenosine is almost always diagnostic, revealing the characteristic “sawtooth” atrial depolarizations. Examination of the jugular pulse or recording of a central venous or right atrial pressure tracing can sometimes reveal the diagnostic atrial “flutter” waves.

The treatment of flutter is the same as that for A-fib. With a success rate greater than 95%, electrical cardioversion is the most effective method of restoring sinus rhythm, even when low doses (50 to 100 WS) of energy are used. Overdrive atrial pacing also effectively terminates this rhythm. Because a high percentage of patients revert to flutter or A-fib after conversion, long-term rate or rhythm control using the same medications as outlined for A-fib is indicated.

**Ventricular Extrasystoles**

Although ventricular extrasystoles are commonly associated with organic heart disease, ischemia, and drug toxicity, they are also observed at very low frequencies in healthy individuals. These autonomous discharges usually occur before the next expected sinus depolarization and are therefore termed PVCs. A PVC is recognized by an abnormally wide QRS complex accompanied by an ST segment and a T wave whose axes are directed
opposite that of the QRS. “Electrically insulated” from the ventricles, the sinoatrial (SA) node continues to discharge independently during the PVC but usually fails to influence the ventricle. Occasionally, when the timing is conducive, a combined supra-ventricular/ventricular electrical impulse may form a “fusion beat.” Because the SA node is not reset by the PVC, the first conducted sinus beat following the PVC appears only after a fully compensatory pause. (A PVC may be interpolated between two sinus beats without a compensatory pause in patients with bradycardia.) It is often difficult to distinguish PVCs from aberrantly conducted supraventricular beats. Factors favoring PVCs are listed in Table 4-3. Aberrantly conducted supraventricular beats (usually in a right bundle branch block configuration) often appear when a short RR interval follows a long RR interval in patients with A-fib or MAT. This “Ashman” phenomenon results from variable, rate-related recovery of the conduction system after depolarization. Occasionally, ventricular extrasystoles are not premature but delayed. These escape beats, usually occurring at a rate of 30 to 40 beats/min, function as a safety mechanism to produce ventricular contraction when normal sinus conduction fails. Ventricular extrasystoles that occur in succession at rates less than 40 beats/min are referred to as “idioventricular.” A rate of 40 to 100 beats/min defines an “accelerated” idioventricular rhythm. For obvious reasons, ventricular escape beats should not be suppressed. The primary treatment of idioventricular rhythm is to increase the SA nodal rate with atropine, isoproterenol, or pacing.

### Table 4-3. Characteristics Favoring Ventricular Arrhythmias over Supraventricular Arrhythmia with Aberrant Conduction

<table>
<thead>
<tr>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rr’ or qR in V1</td>
</tr>
<tr>
<td>Notched QRS complex with R &gt; r’</td>
</tr>
<tr>
<td>QS in V6 or an R/S ratio in V6 &lt; 1.0</td>
</tr>
<tr>
<td>QRS duration &gt; 0.14 s</td>
</tr>
<tr>
<td>Fully compensatory pause</td>
</tr>
<tr>
<td>Fusion beats or capture beats</td>
</tr>
<tr>
<td>AV dissociation</td>
</tr>
<tr>
<td>Extreme left axis deviation (negative leads I and aVF)</td>
</tr>
<tr>
<td>Uniform depolarization rate</td>
</tr>
</tbody>
</table>

The prognosis and treatment of PVCs depends on their cause and frequency. Most PVCs do not require treatment. Indeed, it is clear that pharmacologic suppression of isolated PVCs or minimally symptomatic complex ventricular ectopy in the post-myocardial infarction setting confers a higher likelihood of sudden death. Although some patterns are clearly more dangerous than are others, VT or ventricular fibrillation (VF) often develops without a “warning rhythm.” Historically accepted indications for acute treatment of PVCs in the critically ill include (1) frequent (>5/min) or multifocal PVCs in the setting of cardiac ischemia, (2) VT or frequent PVCs causing angina or hypotension, and (3) an “R on T” configuration (PVC interrupts ascending portion of preceding T wave). The latter indication was once widely accepted but now is more controversial. Common underlying causes of PVCs include ischemia, acidosis, hypoxemia, electrolyte disorders, drugs, and toxins. Surprisingly, “antiarrhythmic” agents have a relatively high frequency (approx. 20%) of worsening existing arrhythmias or causing new rhythm disturbances, the so-called proarrhythmic effect.

The vast majority of PVCs should be ignored, or treatment should be aimed at the underlying cause. Intravenous (IV) lidocaine is the drug of choice for PVCs requiring acute treatment. Amiodarone and procainamide are acceptable parenteral alternatives. Quinidine should not be used in the acute setting because it is sometimes harmful, frequently ineffective, slow to act, and available only as an oral preparation.
Ventricular Tachycardia

VT is defined as three or more consecutive ventricular beats occurring at a rate greater than 100/min (commonly 140 to 220/min). Some clinicians prefer the more stringent definition of ten or more consecutive beats. The beats of VT are recognized by wide QRS complexes with T waves of opposite polarity. The ECG hallmark of VT is AV dissociation (a phenomenon resulting from the independent firing of the SA node and the ventricular focus). Mild beat-to-beat variation in the RR interval is usually present. VT is usually symptomatic and generally occurs in patients with underlying heart disease. “Primary” VT associated with transient myocardial ischemia carries little prognostic significance; however, late or secondary VT occurring several days after infarction is associated with a high likelihood of recurrence and a relatively poor prognosis. The mechanism of VT is the rapid firing of an ectopic ventricular pacemaker or electrical reentry within the His-Purkinje network. Antecedent isolated PVCs are not consistently present, but VT is usually often initiated by a PVC with delayed linkage to the preceding QRS. Occasionally, retrograde atrial depolarization may occur.

VT may take two distinct forms: monomorphic, in which all complexes appear similar, and polymorphic, in which the appearance of complexes changes, as does the QRS axis. Polymorphic VT is often associated with a prolonged baseline QT interval during the preceding sinus rhythm. When polymorphic VT assumes a sinusoidal appearance as if it were revolving about the axe of the isoelectric axis, it is termed torsades de pointes (“the twisting of points”) (Fig. 4-4). This “torsades” rhythm is often associated with administration of a predisposing drug that is given in the high therapeutic or toxic range or used against the background of such additional risk factors as advanced age, female gender, or electrolyte disturbance. Differentiating SVT from monomorphic VT can sometimes be difficult, particularly when supraventricular beats are aberrantly conducted or a bundle branch block is present. Varying S1 heart sounds or cannon A waves in the jugular venous pulse suggest VT, as do capture or fusion beats observed on the ECG. The arrhythmia is likely to be supraventricular if regular, upright P waves occur at appropriate times before each QRS complex. However, if an inverted P wave follows each QRS, VT or junctional tachycardia is more likely. In contrast to reentrant SVTs, VT fails to respond to vagal stimulation and adenosine. The ECG characteristics used to distinguish SVT from VT are helpful but not infallible (Fig. 4-5 and Table 4-3).

FIGURE 4-4. Torsades de pointes as visualized in ECG leads II, III, and AVF.

Regardless of morphology, in the hemodynamically compromised patient VT should be treated with synchronized cardioversion, beginning with 100 WS of monophasic energy or its biphasic equivalent, and then rapidly escalating the energy of the shock until effective.
Therapy of VT should include removal of potentially precipitating agents (Table 4-4) and correction of electrolyte abnormalities, especially hypokalemia and hypomagnesemia. Because it has low toxicity, is inexpensive, and may help, it probably makes sense to administer 2 to 6 g of IV MgSO$_4$ to most patients with VT, especially if polymorphic. (Caution is indicated in patients with renal failure.) Following cardioversion of VT to a stable rhythm, amiodarone, lidocaine, or procainamide is indicated to prevent recurrence. Polymorphic VT is a special case: effective therapy requires shortening the QT interval, usually by accelerating the sinus rate to more than 100 beats/min using atropine, isoproterenol, or ventricular pacing. If the patient with VT is hemodynamically stable, amiodarone, lidocaine, or procainamide may be used as primary therapy. In patients with recurrent VT or recurrent VF, consultation by an electrophysiologist and an ablation procedure or insertion of an implantable cardiodefibrillator should be considered. Unfortunately, effective drug therapy can be discovered for only a minority of patients with recurrent VT.

<table>
<thead>
<tr>
<th>ECG Finding</th>
<th>Waveform</th>
<th>Favors SVT with Aberrancy</th>
<th>Favors VT</th>
</tr>
</thead>
<tbody>
<tr>
<td>rSR' in lead V1 (triphase with 2nd “rabbit ear” taller than 1st)</td>
<td>rS or RS</td>
<td>++++</td>
<td>--</td>
</tr>
<tr>
<td>Rs'r or Rs'r in lead V1 (triphase, with 1st rabbit ear taller than 2nd)</td>
<td></td>
<td>-- --</td>
<td>++++</td>
</tr>
<tr>
<td>Monophasic positive deflection or R' in lead V1</td>
<td></td>
<td>-- --</td>
<td>++</td>
</tr>
<tr>
<td>QR or qR pattern in lead V1</td>
<td></td>
<td>-- --</td>
<td>++</td>
</tr>
<tr>
<td>rS or RS in V6</td>
<td></td>
<td>-- --</td>
<td>++</td>
</tr>
</tbody>
</table>

**FIGURE 4-5.** Helpful ECG clues for distinguishing SVT with aberrancy from ventricular tachycardia.

**Table 4-4.** Drugs Associated with Torsades De Pointes

<table>
<thead>
<tr>
<th>Psychiatric Medications</th>
<th>Antiarrhythmics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Bepridil</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Disopyramide</td>
</tr>
<tr>
<td>Droperidol</td>
<td>Dofetilide</td>
</tr>
</tbody>
</table>
BRADYARRHYTHMIAS

Except when caused by intrinsic disease of the sinus mechanism or conduction system, bradycardia tends to reflect a noncardiac etiology, such as high vagal tone, hypoxemia, hypothyroidism, or drug effect (particularly β-blockers, calcium channel blockers, or digoxin). Bradycardia is usually of little importance in patients with normally compliant hearts, adequate preload reserves, and the ability to peripherally vasoconstrict. However, if stroke volume cannot be increased (e.g., dehydration, pericardial disease, noncompliant myocardium, loss of atrial contraction, depressed contractility), bradycardia may precipitously lower the cardiac output and blood
Sinus Bradycardia

Bradycardia may be physiologic in the heart of a trained athlete and when metabolic demands are reduced (e.g., hypothermia, hypothyroidism, starvation). Conversely, it may be observed transiently during vasovagal episodes in normal individuals or recurrently with minimal stimulation in patients with diseases characterized by dysautonomia (e.g., quadriplegia). Sinus bradycardia (SB) is characterized by normal P wave morphology and 1:1 AV conduction at a rate less than 60 beats/min. The association of SB with inferior and posterior MIs may be related to ischemia of nodal tissue and increased vagal tone. Morphine and β-blockers aggravate bradycardia in such patients. SB does not require treatment unless it is sustained and causes hypotension, light-headedness, pulmonary edema, angina, or ventricular escape beats. However, SB may be a marker of other pathologic processes important to reverse (e.g., hypoxemia, visceral distention, pain, hypothyroidism). SB may be treated with atropine or catecholamine infusions, but both therapies have the potential to increase myocardial O₂ consumption in the setting of myocardial ischemia.

If initial doses of atropine (0.5 to 1 mg IV q 3 to 5 minutes) fail to raise heart rate to an acceptable level, external pacing or infusion of dopamine (5 to 20 μg/kg/min), epinephrine (2 to 10 μg/min), or isoproterenol (2 to 10 μg/min) should be tried as the underlying cause is addressed. Among patients with SB resulting from β-blocker, calcium channel blocker, or digitalis intoxication, these treatments are often ineffective. Specific therapy with antibodies for digitalis intoxication, glucagon in β-blocker overdose, or CaCl₂ (1 to 3 g IV) in calcium channel blocker overdose may be effective. Although not studied in a systematic fashion, the simultaneous infusion of insulin, glucose, and potassium may accelerate heart rate in β-blocker and calcium channel blocker overdose and may improve contractility as well (see Chapter 3).

Atrioventricular Block

First-Degree Atrioventricular Block

In first-degree AV block (1st degree AVB), AV nodal or infranodal conduction is slowed, prolonging the PR interval (>0.2 second). Although 1st degree AVB is itself physiologically unimportant, it may signal drug toxicity or progressive conduction system disease. When newly developed in the ICU, it is usually a temporary phenomenon caused by increased vagal tone or medications. Isolated 1st degree AVB does not require therapy. However, pacing is indicated if 1st degree AVB accompanies right bundle branch block and left anterior fascicular block in the setting of myocardial ischemia or infarct. Complete heart block often follows in such patients. Although external pacing may be effective, the more difficult to initiate, transvenous route usually proves more reliable in capturing the ventricle.

Second-Degree Atrioventricular Block

There are two forms of second-degree AV block (2nd degree AVB), a condition in which some atrial impulses are conducted whereas others are blocked. Mobitz I (Wenckebach) conduction is sequential and progressive prolongation of the PR interval, culminating in periodic failure to transmit the atrial impulse. This pattern often repeats every three or four beats. (Whereas the PR intervals of successive beats progressively lengthen, the RR intervals shorten.) The conduction blockage is almost always within the AV node and is most frequently the result of digitalis toxicity or intrinsic heart disease (e.g., infarction, myocarditis, or cardiac surgery). Because the right coronary artery supplies the AV node in most patients, Mobitz I block often accompanies inferior MI. In this setting, Mobitz I block is usually benign, self-limited, and accompanied by ventricular escape rates of 40 to 50 beats/min. Conversely, Mobitz I block complicating anterior infarction suggests extensive myocardial damage and
a guarded prognosis. Although atropine or isoproterenol may be used to improve conduction, no treatment is usually required. Ventricular pacing is effective but rarely necessary.

Mobitz II AV block originates below the level of the AV node, in the His-Purkinje system predominately supplied by branches of the left anterior descending coronary artery. In contrast to Mobitz I block, the PR interval remains constant but atrial depolarizations are inconsistently conducted. The QRS complex may be prolonged if the His bundle is the site of blockade. Mobitz II block is usually not transient and, because it often progresses to symptomatic AV block of higher degree, almost always requires treatment. Mobitz II block with 2:1 conduction is difficult or impossible to separate from Mobitz I block in which every other P wave is nonconducted. (One helpful clue may be that QRS prolongation is more common in Mobitz II block.) Atropine fails to influence the infranodal site of blockade, making transvenous pacing necessary in most cases (see following).

**Third-Degree Atrioventricular Block**

During complete or third-degree AV block (3rd degree AVB), the atria and ventricles fire independently, usually at different but regular rates. 3rd degree AVB may result from degenerative myocardial disease or myocarditis, MI, or infiltration of the conducting system (e.g., sarcoidosis, amyloidosis). Toxic concentrations of digitalis and other drugs may also produce 3 degree AVB. On physical examination, AV dissociation produces a varying first heart sound and cannon A waves in the jugular venous pulse, the result of occasional simultaneous atrial and ventricular contractions. Blockage of the AV node itself produces a “narrow complex” junctional rhythm at a rate of 40 to 60 beats/min and usually results from MI. In most cases, it is transient and asymptomatic. On the other hand, infranodal AV block, a pattern associated with a wide QRS (>0.10 second), is almost always symptomatic because it tends to produce slower heart rates (30 to 45 beats/min). The inherent instability of pacemakers originating distal to the AV node renders infranodal 3 degree AVB worthy of treatment, regardless of rate. Immediate insertion of a transvenous pacemaker is indicated.

**ANTIARRHYTHMIC DRUGS**

Antiarrhythmic therapy is far from ideal because antiarrhythmics fail to suppress the rhythm disorder in approximately 50% of cases, and in many situations rhythm control does not improve outcome. Most antiarrhythmic drugs have a narrow therapeutic window with a high incidence of gastrointestinal and central nervous system side effects. Paradoxically, antiarrhythmic drugs exacerbate the underlying problem or cause new arrhythmias in as many as 20% of treated patients (“proarrhythmic” effects). Moreover, preoccupation with the drug management of physiologically insignificant arrhythmias may distract from addressing important underlying problems (e.g., ischemia, electrolyte disturbance, heart failure, thyrotoxicosis, or drug intoxication). Normalizing arterial oxygenation, pH, potassium, and magnesium often improves or abolishes the arrhythmic tendency. In hypotensive or pulseless patients with tachyarrhythmias, immediate electrical cardioversion (not pharmacotherapy) is the appropriate initial treatment. Synchronized cardioversion is the preferred method, except in VF where unsynchronized shock is used. Surprisingly, in the setting of ischemic heart disease, only β-blocking agents have convincingly reduced mortality, and their beneficial effect is not likely related to arrhythmia suppression alone. A simplified version of a standard classification system for antiarrhythmic drugs is presented in Table 4-5, and an overview of drugs used in the treatment of symptomatic arrhythmias is presented in Table 4-6. For patients with sustained VT or recurrent VF, automatic implantable pacer/defibrillators take precedence over and may even obviate drug therapy, reducing annual mortality to 1% to 2%. Unfortunately, an invasive procedure is required for placement, the procedure is
Table 4-5. Classification of Commonly Used Antiarrhythmics

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of Action</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Depress conduction</td>
<td>Quinidine</td>
</tr>
<tr>
<td></td>
<td>Accelerate repolarization</td>
<td>Procainamide, Disopyramide</td>
</tr>
<tr>
<td>Ib</td>
<td>Depress conduction</td>
<td>Lidocaine</td>
</tr>
<tr>
<td></td>
<td>Accelerate repolarization</td>
<td>Phenytoin, Tocainide, Mexiletine</td>
</tr>
<tr>
<td>Ic</td>
<td>Markedly reduce conduction</td>
<td>Flecainide, Encaidine</td>
</tr>
<tr>
<td>II</td>
<td>Block β-receptors</td>
<td>Propranolol, Esmolol, Metoprolol</td>
</tr>
<tr>
<td>III</td>
<td>Prolong repolarization</td>
<td>Amiodarone, Bretylium, Sotalol</td>
</tr>
<tr>
<td>IV</td>
<td>Block Ca(^{2+}) slow channels, decrease automaticity and nodal conduction</td>
<td>Verapamil, Diltiazem, Nicardipine</td>
</tr>
</tbody>
</table>

Table 4-6. Treatment of Symptomatic Arrhythmias

<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>Primary Treatment(^a)</th>
<th>Alternative or Supplemental Measures</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>Cardioversion</td>
<td>Rate control with digoxin, diltiazem, esmolol, or amiodarone, procainamide</td>
<td>Inhibit recurrence with Ca(^{2+}) blocker or β-blocker</td>
</tr>
<tr>
<td>AV re-entrant and AV nodal re-entrant tachycardia</td>
<td>Vagal stimulation Adenosine</td>
<td>Ca(^{2+}) blocker, β-blocker, or digoxin</td>
<td>Cardioversion if drugs fail or reversal urgent</td>
</tr>
</tbody>
</table>
Multifocal atrial tachycardia  Correction of metabolic or cardiopulmonary cause  Ca\textsuperscript{2+} blocker or β-blocker  Drugs slow the rate but rarely reestablish sinus mechanism

Bradycardia  Removal of offending medications, correction of hypoxemia  Catecholamine infusion  Hypoxemia and vagal reflexes are common precipitants

Supranodal  Infranodal  Atropine/oxygen Isoproterenol/pacing

Ventricular premature contractions  Lidocaine  Procainamide  Treatment often unnecessary

Monomorphic ventricular tachycardia  Cardioversion  Lidocaine, procainamide, sotalol, amiodarone

Polymorphic ventricular tachycardia  Cardioversion  Isoproterenol  Magnesium, overdrive pacing

Ventricular fibrillation  Cardioversion  Lidocaine  Success rate correlates inversely with duration

Digitoxic rhythms  Digitalis antibodies  Phenytoin, procainamide, lidocaine, KCl, propranolol

\textsuperscript{a}Correction of hypoxemia, hypotension, disturbances of pH and electrolytes (Ca\textsuperscript{2+}, Mg\textsuperscript{2+}, K\textsuperscript{+}) is a key element of therapy for all arrhythmias.

**Specific Antiarrhythmic Drugs**

**Amiodarone**

Amiodarone is a highly effective antiarrhythmic for a wide variety of supraventricular and ventricular rhythm disturbances. At one time, amiodarone was used in high doses only for refractory life-threatening ventricular arrhythmias, in large part because of its significant toxicities. Now, lower, less-toxic doses have been shown to be effective for a variety of supraventricular arrhythmias. During cardiac arrest, 300 mg given rapidly intravenously is usually the dose indicated. For serious ventricular arrhythmias, 150 mg given by rapid IV infusion over 15 minutes may be effective. For less critical ventricular arrhythmias, a loading dose of 360 mg given as a 1-mg/min loading infusion (6 hours) is...
followed by an additional 540 mg given as a 0.5-g/min infusion. AVNRT, AVRT, A-fib, and flutter are controlled in up to 70% of patients, and ventricular arrhythmias may be controlled almost as frequently. Amiodarone may be the most effective agent for controlling A-fib, but questions persist about its long-term safety, and many recipients discontinue therapy because of toxicity. The most common side effects are gastrointestinal and neurological. Pulmonary toxicity is a well-recognized, potentially fatal complication of higher doses, especially in patients with preexisting lung fibrosis. On its own, amiodarone may induce

SA or AV nodal blockade as well as infranodal conduction system disorders. Unpredictable interactions can also occur with other antiarrhythmics. Amiodarone routinely increases plasma levels of digoxin, quinidine, procainamide, and flecainide and potentiates the anticoagulant effect of warfarin.

**β-Adrenergic Blockers**

A variety of β-adrenergic blocking drugs are available that differ with respect to speed of onset, receptor selectivity, duration of action, and side effects. The prototype is propranolol, whose primary actions are shared by most members of the class. Propranolol, a nonspecific β-blocker, is a negative inotrope and chronotrope that decreases the rate of SA node depolarization and conduction velocity. Although useful in states of catecholamine excess (e.g., pheochromocytoma, hyperthyroidism, cocaine toxicity), sudden β-blockade may produce disastrous results in patients who depend on catecholamine stimulation for compensation. Such problems are likely to arise in patients with volume depletion, impaired cardiac contractility, or stroke volume limited by hypertrophy or constriction. Cardioselective β-blockers (e.g., metoprolol, carvedilol) are usually better tolerated. β-Blockade helps slow the rate in AVNRT, AVRT, A-fib, and flutter. These drugs are less than ideal choices for treating most ventricular arrhythmias, except when these disturbances are provoked or exacerbated by tachycardia or ischemia. In emergency situations, propranolol may be administered in IV doses of 0.5 to 1 mg every 10 minutes. Contraindications include severe bradycardia or high-grade AV block, advanced heart failure, obstructive lung diseases, or digitalis toxicity. β-blocking drugs may aggravate coronary spasm. When selecting a β-blocker, the desired duration of action should be a key consideration. The antiarrhythmic and antihypertensive effects of a single dose of atenolol may last for 24 hours. Conversely, the ultra-short action of esmolol may help in the acute management of supraventricular tachyarrhythmias without depressing myocardial function for protracted periods.

**Calcium Channel Blockers**

Calcium channel blockers often convert AVNRT and AVRT to sinus rhythm and slow the ventricular response of A-fib and flutter but rarely convert MAT, A-fib, or flutter to sinus rhythm. Verapamil has the longest track record, and IV doses of 2.5 to 5 mg at 5- to 10-minute intervals are usually promptly effective. Verapamil must be given with extreme caution, however; even with commonly used doses, high-grade AV block (occasionally asystole) may result. (Asystole is more common in VT than in SVT.) Because of its vasodilating and contractility impairing effects, hypotension occurs commonly in the volume-depleted and elderly; however, this troublesome effect can often be avoided by pretreatment with IV calcium gluconate. Diltiazem is somewhat safer and more predictable in its actions.

**Digitalis**

The major use of digitalis is to slow AV conduction in A-fib and flutter, especially in patients with impaired ventricular function. In this role, it is usually given in 0.125- to 0.25-mg doses IV every 4 to 6 hours until the ventricular response rate is less than 100/min. (The dose is titrated to the desired degree of AV block, with less regard for “therapeutic levels.”) Nonetheless, levels above 3 ng/mL are poorly tolerated and usually not necessary. Heart block, increased myocardial irritability,
gastrointestinal distress (nausea and vomiting), and central nervous system disturbances (confusion, visual aberrations) are the most common side effects.

**Lidocaine**

Lidocaine, a type I-b antiarrhythmic, effectively suppresses ventricular irritability but has little effect on supraventricular arrhythmias. In the setting of myocardial ischemia, it is probably more effective than procainamide for VT, with the reverse being true for non-ischemia-related VT. Because a survival benefit has not been demonstrated and side effects are common, prophylactic therapy in myocardial ischemia is not recommended. Lidocaine distributes into multiple compartments; therefore, it requires several loading doses to achieve and maintain effective serum concentration. Loading is usually accomplished by giving two to three decremental doses (e.g., 100, 75, and 50 mg) spaced about 10 minutes apart. For similar reasons, a modified drug bolus should accompany increased infusion rates when correcting an inadequate serum concentration. Lidocaine doses should be reduced in the elderly and in patients with heart failure, shock, or liver disease (see Chapter 15). No adjustment is needed for renal dysfunction, but patients should be closely monitored after institution or withdrawal of drugs interfering with the hepatic metabolism of lidocaine.

(e.g., cimetidine, propranolol). Neurological toxicity, including confusion, lethargy, and seizures, emerges with lidocaine levels greater than 5 μg/mL. Lidocaine may also exacerbate the neuromuscular blocking effects of paralytic drugs. Hemodynamic effects are usually inconsequential but include mild depression of blood pressure and cardiac contractility as well as a tendency to accentuate second or third degree heart block. Because of its multicompartment distribution, lidocaine declines slowly (over 6 hours) after abrupt termination, making tapering of the drug unnecessary.

**Phenytoin**

Phenytoin is a rarely used type 1b antiarrhythmic effective in treating digitalis-induced ventricular tachyarrhythmias. Phenytoin shortens the QT and PR intervals and increases AV block. Typical loading doses are 10 to 20 mg/kg, but they must be given slowly (<50 mg/min) as the rhythm is monitored. The drug and its solvent, propylene glycol, may provoke serious arrhythmias or hypotension during rapid administration. Phenytoin lowers blood pressure by decreasing cardiac output and systemic vascular resistance. Ataxia is the major toxicity, occurring at levels greater than 20 mg/dL. Phenytoin potentiates the effects of other drugs that are highly protein bound (e.g., warfarin).

**Procainamide**

Procainamide is a type la antiarrhythmic, in many ways similar to quinidine, useful for both supraventricular and ventricular arrhythmias. It effectively controls PVCs and VT and may convert supraventricular arrhythmias to sinus rhythm. Procainamide is more effective than lidocaine for non-ischemia-related VT. Like other type la drugs, procainamide may accelerate the ventricular rate in A-fib or flutter unless conduction is slowed with digitalis or β-blockers or calcium channel blockers. In the average-sized patient, a total loading dose of 1 g is given by injecting sequential boluses of 100 mg every 5 minutes. When continuous therapy is required, loading may be followed by an infusion of 2 to 6 mg/min. Procainamide is a vasodilator and negative inotrope, thereby acting to decrease blood pressure and contractility. Both the QRS and QT intervals of the ECG often increase modestly, and procainamide may precipitate torsades de pointes. Procainamide is less likely than quinidine to cause gastrointestinal distress but over long periods, can induce a lupus-like syndrome in as many as 20% of patients. A positive antinuclear antibody (ANA) develops in approximately 50% of all patients using the drug chronically, effects that are reversible with discontinuation of therapy. Rare cases of hemolysis or agranulocytosis have been reported.
**Sotalol**

Sotalol increases the action potential duration and has β-blocking properties and therefore is a reasonable drug to control AVNRT, and is moderately effective for A-fib and flutter. In contrast to other β-blockers and AV nodal blocking agents (e.g., digitalis, verapamil), sotalol can also influence an AVRT that utilizes an accessory pathway (e.g., Wolff-Parkinson-White syndrome). Sotalol is also one of the few agents demonstrated to decrease the frequency of sustained VT and VF and their associated mortality. Because of its QT-prolonging effects, use in the setting of hypokalemia or hypomagnesemia or combination with other drugs known to prolong the QT interval is unwise. Sotalol's QT-prolonging actions can precipitate torsades de pointes; hence, it should probably be initiated during ECG monitoring in a hospital.

**ELECTRICAL CARDIOVERSION**

**External Cardioversion**

Electrical shock terminates arrhythmias by depolarizing the entire myocardium simultaneously, allowing a stable pacemaker to emerge (see Chapter 20). Electrical cardioversion is indicated for pulseless or hypotensive tachyarrhythmias and VF. Synchronized cardioversion is the preferred method whenever an organized rhythm is present, but is superfluous for VF. Synchronization times the electrical discharge to occur slightly after the R wave (a “nonvulnerable” point in the cardiac cycle where shock is unlikely to induce VF). To trigger the discharge synchronization requires monitoring of an ECG lead that demonstrates a tall R wave (usually lead I or II). Rarely, tall, steeply sloping T waves may trigger discharge at inappropriate times. If possible, patients undergoing elective cardioversion should take nothing by mouth for 8 hours before the procedure to minimize the risk of aspiration. Trained personnel should be present to monitor airway patency, ventilation, oxygenation, and level of sedation. Benzodiazepines, ultra-short-acting barbiturates, propofol, or short-acting synthetic narcotics can produce sufficient sedation and amnesia for patient comfort. Hypoxemia, electrolyte disorders (especially hypokalemia and hypomagnesemia), and thyroid function should be corrected before the elective synchronized cardioversion. Digitalis preparations should be withheld for 24 to 48 hours before the procedure to minimize risks of postcardioversion arrhythmias.

The appropriate dose of electricity depends on the underlying rhythm and if a monophasic or biphasic device is used. Unsuccessful attempts should be followed by subsequent shocks with incremental energy. Being relatively unstable, flutter may convert with as little as 5 J (WS), but the more stable A-fib may require 50 WS or more. Patients with reentrant SVT often require 50 to 100 WS, and VT often requires 200 WS for conversion. In patients with AVNRT and AVRT, electrical “fatigue” of the SA or AV nodes may delay recovery of normal conduction and automaticity. For this reason, the physician should be prepared to initiate transcutaneous pacing and immediately insert a temporary transvenous pacemaker after reversal of the arrhythmia. Adverse effects of cardioversion include skin burns and disorders of conduction and repolarization. The myocardium may be dysfunctional for a variable period afterward. Creatine phosphokinase (CPK), troponin, and lactic dehydrogenase (LDH) may rise slightly. The most dreaded complication of cardioversion is systemic embolization, a problem most commonly seen in nonanticoagulated patients with dilated cardiomyopathy, mitral stenosis, or chronic A-fib.

**Implantable Defibrillators**

The technology of implantable pacer/defibrillators (ICDs) is changing too rapidly to allow an enduring discussion
of individual devices. Improved longevity, smaller size, better software, and the development of combined pacing/defibrillating devices have dramatically advanced the utility and popularity of these tools. It is clear that mortality can be reduced by insertion of an ICD in patients with sustained impairment of ventricular function and sustained VT, compared to chemical antiarrhythmic therapy.

<table>
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<tr>
<th>Category</th>
<th>1 Chamber(s) Paced</th>
<th>2 Chamber(s) Sensed</th>
<th>3 Response to Sensing</th>
<th>4 Rate Modulation</th>
<th>5 Multisite Pacing</th>
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**PACEMAKERS**

**Permanent Pacemakers**

A complete discussion of the issues surrounding permanent pacemakers is well beyond the scope of this book, but the ICU physician must have a basic understanding of pacer terminology and be able to troubleshoot simple problems. Fortunately, standardized nomenclature has emerged to describe pacer functions (see Table 4-7). The most basic pacers can be described by the chamber(s) that is paced, the chamber(s) from which sensing takes place, and what effect a sensed patient depolarization has on the pacer. For example, a pacer that has ventricular pacing, has ventricular sensing, and is inhibited by a spontaneous ventricular depolarization would be termed a VVI pacer. Along the same lines, a DDD pacer has atrial and ventricular pacing and sensing leads. The atrial lead is stimulated first, and if a ventricular depolarization does not occur within the normally expected conduction time, then the ventricle is paced. Spontaneous atrial and ventricular signals are capable of inhibiting the pacing function. Sophisticated devices now are capable of detecting increased patient activity or breathing and accelerating the pacing rate, so-called rate modulation. In addition, complex pacers capable of coordinating atrial and ventricular contractions and of stimulating simultaneous contraction of both ventricles improve long-term outcomes.

Regardless of the kind of permanent pacer present, troubleshooting is usually straightforward and begins with a chest radiograph and 12-lead ECG. The chest film usually can demonstrate lead fracture or electrode migration. The ECG helps parse problems into those of sensing or pacing. The first step is to look for a pacer “spike” and see if it captures (i.e., depolarizes) the chamber. The observation of capture at a reasonable rate all but rules out pacer malfunction. If there is capture but at an unsuitably slow rate, mechanical failure of the pacer (e.g., lead fracture, pulse generator malfunction) or “oversensing” are likely explanations. Oversensing is pacer inhibition by inappropriate electrical signals such as those of other ECG components (e.g., T waves), of external electromagnetic interference, or of muscle artifact. If the capture rate is too rapid, undersensing may be to blame.
Undersensing occurs when the pacing generator fails to appropriately recognize cardiac electrical signals as a result of lead fracture, or changes in electrical transmission between the lead and the myocardium (e.g., myocardial infarct, fibrosis, electrolyte imbalance, drug intoxication). Failure to capture or pace is often a mechanical device failure but is appropriate if the patient’s intrinsic rhythm is sufficient to completely inhibit pacer output. Placing a magnet over the pacer will differentiate between oversensing and mechanical failure. In the former case, the pacer will operate normally in an asynchronous mode; in the latter case, the pacer continues to malfunction.

**Resynchronization Pacing**

Although device selection is rarely made by the critical care physician, intensivists should be aware of the potential value of implanted resynchronization devices for boosting the output of failing hearts characterized by dilation and the widened QRS complexes characteristic of left bundle branch block. These biventricular (multisite) pacers improve ventricular synchrony and may aid in the prevention of cardiac dilation and remodeling that later predispose to serious arrhythmias and risk for sudden cardiac arrest. Defibrillating functions may also be incorporated.

**Temporary Pacemakers**

Because temporary transvenous pacemakers are frequently inserted in the ICU, understanding their use and associated problems is essential. Temporary pacemakers are indicated for (1) high-grade (especially symptomatic) AV block, (2) overdrive suppression of refractory atrial tachyarrhythmias, (3) suppression of torsades de pointes resulting from bradycardia, (4) sick sinus syndrome, and (5) control of post-cardiac surgery arrhythmias. In emergent situations, noninvasive transthoracic pacing is worth trying but often fails to capture the ventricle. More likely to be successful is insertion of a transvenous pacing catheter. Effective temporary pacing requires that the catheter electrodes firmly contact the endocardium of the right ventricle. When optimally positioned, the pacer will sense the occurrence of native electrical discharges and achieve ventricular capture using a very low energy pulse. Although complex pacemakers capable of sequential AV pacing are available, these are rarely necessary in the ICU and often do not function properly when inserted emergently. A simple ventricular pacer will suffice in almost all cases.

Three basic kinds of pacing conductors are available: semistiff dedicated pacing “wires,” balloon-tipped pacing catheters, and pacing-capable pulmonary artery catheters. All three are bipolar, that is, they contain both a distal cathode and proximal anode. (When electively inserting a pulmonary artery catheter in a patient with left bundle branch block, a pacing-capable catheter should be considered because insertion can (rarely) precipitate complete heart block.) The stiff pacing wires may be the most difficult to place emergently but, once in place, are usually the most stable. By contrast, the easier-to-place, flow-directed balloon catheters are the least stable.

Although the right internal jugular and left subclavian sites are the easiest access points, brachial or femoral veins can be used for pacer insertion. Fluoroscopic guidance can be helpful to properly position the catheter, but often cannot be arranged emergently. Therefore, in most cases the pacing lead is inserted using only ECG guidance. (Skilled cardiac ultrasound may also be helpful.) The ECG can be used in two ways to guide placement. For patients with an underlying rhythm, the distal electrode can be connected to the V1 lead of the ECG while standard limb leads are attached to the patient. The pacer wire is then slowly advanced, while continuously monitoring the ECG signal. While the catheter is in the superior vena cava, a small negative atrial deflection will be noted. If the catheter “bypasses” the heart, into the inferior vena cava, the atrial deflection becomes positive. If that happens, the catheter needs to be withdrawn and readvanced. When the right ventricle is finally entered, a large ventricular signal will be sensed. Advancing the catheter further results in an “injury” current in the monitored lead when the ventricular wall is encountered.
(These findings are most evident if simultaneous recording of one or two limb leads is performed.) The pacer is then disconnected from the ECG machine, and an attempt to pace the ventricle is made. In patients without a ventricular rhythm, the surface ECG is merely monitored as the pacing wire or catheter is blindly advanced toward the right ventricle with the pacing generator discharging in an asynchronous mode. When capture occurs, the ECG demonstrates a wide QRS ventricular depolarization.

To generate depolarizations, the bipolar electrodes are connected to an external pacing generator. The simplest of these devices has three adjustments: discharge rate, output pacing current (in milliamps), and sensitivity (the electrical strength, in millivolts, of intrinsic cardiac current necessary to inhibit firing of the pacer). In asystolic patients, the pacing catheter should be inserted with the generator in the asynchronous mode, with a high output (5 to 10 mA) at a rate of approximately 100 beats/min. Using the highest output current maximizes the chance of capture, and using a rate of 100 beats/min provides a sufficiently frequent spike to make it easily recognizable. In addition, a rate of 100 beats/min is almost always sufficient to generate an adequate cardiac output when capture occurs. Monitoring the surface ECG will initially reveal a narrow pacing spike until the catheter encounters the right ventricular wall. Upon capture, the ECG will show the typical bundle branch block pattern of depolarizations originating in the ventricle. Very rarely, the pacing electrode will lodge in the right atrium producing a normal narrow QRS complex.

After insertion, the generator should be adjusted to achieve three major goals: (1) a heart rate sufficient to meet cardiac output requirements, (2) a minimized pacing threshold (current necessary to achieve capture), and (3) a sensitivity threshold that prevents simultaneous patient and pacer discharge. If spontaneous electrical activity is present, the pacer should usually be operated in the “demand” mode, discharging only when intrinsic activity is not sensed. Initially, the sensitivity setting should be set on its least value (usually 1.5 mV) and then gradually increased until the pacer fails to sense the intrinsic beats. The point at which the pacer fails to recognize intrinsic electrical activity is the “sensitivity threshold.” With regard to pacer output, the minimum current necessary to capture the ventricle should be used so as to minimize endocardial injury. This “pacing threshold” is determined by reducing the output setting from the initial 5- to 10-mA range until the pacer fails to capture the ventricle. Ideally, capture can be achieved with outputs as low as 0.5 mA. Because a patient's sensitivity to pacing varies with a variety of factors, including catheter position, it is customary to set the output at a value two to three times the capture threshold. Once pacing and sensitivity thresholds have been set, the rate can be adjusted to provide an acceptable cardiac output.

Several problems may occur with emergent temporary pacemaker placement. Although unusual, the pacing catheter can perforate the thin-walled right atrium or ventricle. Perforation can occur at the time of insertion but more commonly is delayed for hours to days after placement. Its detection is signaled by an increase in the pacing threshold or failure to capture. Electrical discharges may be accompanied by chest or shoulder pain or the development of hiccups as the diaphragm is stimulated by the pacer. Physical exam at that time may reveal a new pericardial friction rub or tamponade; chest radiograph or echocardiogram confirms puncture by demonstrating a shifted electrode position or accumulated pericardial fluid. The pacer can provoke atrial and ventricular arrhythmias, especially if it is coiled in the ventricle or placed into the right ventricular outflow tract. Again, malposition can be detected by plain chest radiograph. As may occur with any indwelling catheter, infection or thrombosis may develop. Both risks relate predominately to the duration of the catheterization and sterility of insertion.

Because of the technical expertise and time necessary to insert an IV pacer, transcutaneous pacing technology has been developed. Although transcutaneous devices are less likely than transvenous devices to achieve ventricular capture, when they are effective, pacing can be achieved in seconds instead of minutes. Thus transcutaneous pacing is best viewed as a temporizing measure until transvenous pacing is achieved or the underlying cause of bradycardia is reversed.
Pacing with an external pacer is initiated by firmly applying the pacing/defibrillating pads to the chest with the negative electrode on the anterior chest wall at the left sternal border (V3 position). Ideally, the positive electrode is placed on the back between the spine and scapula directly opposite the negative pad. The pacing rate and output (mA) are variable, but unlike internal pacers, the sensing threshold is typically not adjustable. Starting at an output of 5 mA and increasing the output at 5 mA intervals until capture is achieved or discomfort becomes intolerable is a reasonable strategy for the conscious bradycardic patient. For the unconscious patient, starting at a maximal output setting (typically 200 mA) until capture is achieved and then decreasing the output until capture is lost is a prudent strategy. When “electrical capture” is seen on the ECG, the patient's pulse and blood pressure should be checked to ensure adequate cardiac output. Setting the demand rate near 100 will almost always be sufficient to meet metabolic demands if capture is achieved.

External pacing has two major problems: failure to capture and pain. Obese patients, those with pericardial effusion, those with severe emphysema, and those receiving mechanical ventilation may be more difficult to pace. Improper position of the electrodes or poor skin-electrode contact can also lead to pacing failure. In addition, capture is less likely if begun long after the onset of bradycardia or asystole. Pain is a common problem for the conscious patient. Discomfort can be improved with simple sedatives and analgesics and by increasing the pulse duration.

**SUGGESTED READINGS**


Chapter 5
Respiratory Monitoring

• Key Points

1. Although pulse oximetry is an invaluable clinical tool, it provides a signal-averaged number, the output of which lags slightly behind the actual physiologic value of interest. Pulse oximetry is influenced by extraneous rhythmic vibration, carbon monoxide, and methemoglobin. Even if the recorded pulse rate correlates exactly with an independently measured value, oximetry loses accuracy when local perfusion is compromised or true arterial saturation falls to less than 80%.

2. After a step change in ventilation, arterial carbon dioxide concentration approaches steady-state equilibrium less quickly than does the arterial oxygen tension because the storage reservoir of the body for CO₂ is far larger than that for O₂.

3. Exhaled gas capnometry provides useful and noninvasive information regarding CO₂ production, dead space fraction, and trends in ventilation.

4. Lung compliance is influenced by the number of patent alveolar units, by their elasticity, and by the characteristics of the surrounding chest wall. The static and dynamic pressure-volume curves of the respiratory system can provide useful information unavailable from simpler indices, such as tidal compliance and driving pressure.

5. The mechanics of breathing (resistance and compliance) are most easily assessed during passive inflation with a known constant flow, using an end-inspiratory pause. During active breathing or when the chest wall is stiff, the mechanical properties of the lung can be assessed if pleural pressure is recorded using an esophageal balloon.

6. Auto-PEEP, usually a reflection of dynamic hyperinflation during passive breathing, contributes to the work of active breathing and to patient-ventilator asynchrony. Because auto-PEEP varies from site to site throughout the lungs of a diseased patient, the externally measured value may not accurately reflect the degree of local overdistention. In obstructive diseases (asthma, chronic obstructive lung disease), the end-inspiratory plateau pressure indicates the degree of hyperinflation better than does auto-PEEP itself.

7. The flow tracing can be used to detect (but not quantify) auto-PEEP, flow limitation, airway secretions, and poor coordination between the tidal rhythms of patient and ventilator. The zero-flow points of the flow tracing partition the ventilatory cycle into its inspiratory and expiratory phases. The airway pressure tracing complements the flow tracing, helping to detect and quantify the work of breathing. Pressure-volume and flow-volume displays of the same information help in targeted applications.

8. As an index that tracks mean alveolar pressure and lung volume, mean airway pressure recorded under passive conditions is an important determinant of arterial oxygenation, the back pressure to venous return, and the tendency for gas leakage after barotrauma. Mean airway pressure alone has limited value during active breathing and underestimates mean alveolar pressure when expiratory pressure losses exceed inspiratory pressure losses.

9. Respiratory muscle dyssynchrony, elevations in the $P_{0.1}$, and an excessive frequency to tidal volume ratio are helpful indicators of respiratory muscle overload and incipient muscle fatigue.

10. Breathing pattern variability, the CO₂ challenged $P_{0.1}$, the ratio between spontaneous tidal volume and vital capacity, the frequency to tidal volume ratio, and the ratio between minute ventilation and maximum
Data relevant to the output, efficiency, capacity, and reserve of the respiratory system guide appropriate management during cardiorespiratory failure. Monitoring techniques can be classified conveniently into those that characterize pulmonary and systemic exchange of respiratory gases, ventilatory capability, and respiratory mechanics (flow, pressures, and breathing workload). In many centers, lung and diaphragm are now being probed, imaged, and monitored by ultrasonography (US), electromyography (EMG), and electrical impedance tomography (EIT).

**MONITORING GAS EXCHANGE**

**Blood Gas Analysis**

Analysis of arterial blood gases (ABG) provides data that are fundamental to the diagnosis of respiratory and metabolic disturbances and to assessment of therapeutic interventions. Central venous blood gas analysis complements (and for some purposes substitutes for) such information. Although certain inferences can be made from the blood gas data alone, full interpretation and appreciation of their implications for decision making require knowledge of the clinical context, serum electrolyte concentrations, and, in certain settings, the serum albumin and lactate concentrations as well.

**Arterial \( O_2 \) Tension and Saturation**

The physiologic significance of hypoxemia depends on chronicity, compensatory mechanisms, hypoxic ventilatory response, and tolerance of vital organs most at risk—chiefly, the heart and brain. Clearly, a patient with critical coronary stenosis, acute cor pulmonale, or symptomatic cerebrovascular compromise should be kept adequately well saturated while avoiding hyperoxia, as should patients with ongoing dyspnea, symptomatic circulatory inadequacy, or severe anemia. Conversely, maintaining less than full saturation may be appropriate for patients who depend chronically on moderate hypoxemia to allow CO\(_2\) retention, for those with intact compensatory mechanisms, and for patients in whom full \( O_2 \) saturation can be achieved only at the expense of high fractions of inspired oxygen or ventilating pressure. Quite recently, devices intended to monitor tissue oxygenation and perfusion adequacy have been released for clinical use. All have limitations for assessing perfusion status of interior zones of vital organs. Near-infrared spectrophotometry and sublingual PCO\(_2\) monitoring show considerable promise, but though they are theoretically appealing, the clinical value of these noninvasive instruments has yet to be determined.

In the absence of carbon monoxide, methemoglobin, or abnormal hemoglobin, arterial \( O_2 \) saturation can be estimated with acceptable accuracy from the \( PaO_2 \) and \( pH \) alone—at least near the upper plateau of the oxyhemoglobin relationship. If knowing the arterial \( O_2 \) content is required, or if carboxyhemoglobin or methemoglobin concentrations are high, direct analysis by co-oximetry must be requested. (This is particularly important when analyzing mixed venous \( O_2 \) saturations.) Whether to “temperature correct” the analyzed specimen is debatable, depending somewhat on the purpose to which such information is put. For example, temperature correction would seem appropriate if the oxygen-exchanging efficiency of the lung were the primary question, whereas the need to correct \( SaO_2 \) for temperature is more debatable when tissue \( O_2 \) adequacy is the concern. Individual hospital laboratories have different practices and reporting policies with regard to these issues.
Acid-Base Status, pH, and PaCO₂

Hydrogen ion concentration must be regulated carefully to preserve enzyme function. Normally, acids are generated by the hydration of CO₂ (“respiratory” acid) and by other processes of metabolism (“metabolic acids”—primarily phosphate, sulfate, and lactate). In disease states, hydrogen ion concentration can rise secondary to the production of excess lactate (ischemia, hypoxemia), generation of ketoacids (diabetes, starvation), toxic ingestion of certain alcohols or drugs (e.g., metformin), or failure of the body to excrete or metabolize the generated load of hydrogen ion (ventilatory failure, kidney dysfunction, or liver disease).

Occasionally, sufficient hydrogen or bicarbonate ion is lost in the urine or stool or is intentionally suctioned from the gastrointestinal tract to affect acid-base balance. To address such disorders, the clinician must understand the primary determinants of acid-base homeostasis and deftly interpret pH, PaCO₂, and components of the blood gas report alongside the electrolyte profile (to calculate anion gap).

The body defends against radical changes in pH primarily by regulating its two pathways for eliminating acid: respiratory and renal. (A full discussion of acid-base principles is provided in Chapter 12.) The Henderson-Hesselbach equation for the bicarbonate buffer system relates pH to the concentrations of bicarbonate and PaCO₂:

\[
pH = 6.1 + \log \left( \frac{[HCO₃^-]}{[0.03 PaCO₂]} \right)
\]

In this expression, knowledge of any two variables enables calculation of the third. In blood gas analyses, PaCO₂ (lung excreted) and pH are measured, and \([HCO₃^-]\) (kidney excreted) is estimated. Once formed, hydrogen ions are neutralized partially by combining with bicarbonate ion (producing CO₂) and by reversible oxidation of protein. The bicarbonate buffer system:

\[
CO₂ + H₂O \leftrightarrow H₂CO₃ \leftrightarrow H^+ + HCO₃^-)
\]
generates CO₂ when H⁺ is added to the extracellular fluid. The rising CO₂ and H⁺ concentrations stimulate the respiratory center in an attempt to limit hypercapnia, effectively eliminating H⁺ by driving the preceding equation leftward. Over time (generally several days are required), the healthy kidney will adapt to hypercapnia or hypocapnia by adjusting the bicarbonate level to help restore the Henderson-Hasselbalch-defined 20:1 normal ratio between bicarbonate concentration and the product of PaCO₂ and its solubility coefficient (0.03).

Respiratory compensation for metabolic disturbances is generally incomplete and occurs more reliably and vigorously in response to metabolic acidosis than to metabolic alkalosis.

Despite its functional importance, this bicarbonate buffer system is not the only one available—skeletal calcium and certain proteins, chiefly hemoglobin, also play a significant role. Thus, a rising [H⁺] is partially buffered by hemoglobin, as well as by [HCO₃⁻], giving rise to a generally small discrepancy between the difference in [HCO₃⁻] relative to normal (24 mEq/dL) and the calculated base excess or deficit, which quantifies the magnitude of the metabolic disturbance or compensation. An acutely rising PaCO₂ tends to generate bicarbonate, as a portion of the H⁺ formed in the hydration of CO₂ that is buffered by hemoglobin; the opposite occurs during hyperventilation. Thus, even in the absence of renal activity, the acutely rising PaCO₂ of pure hypoventilation is accompanied by a gently rising [HCO₃⁻]; an acutely falling PaCO₂ is accompanied by a gently falling [HCO₃⁻].
Definitions

Acidosis and alkalosis—the underlying processes that contribute to the pH status—may be pathogenic or compensatory. The normal ranges for arterial pH and PaCO$_2$ are 7.38 to 7.44 and 35 to 45 mm Hg, respectively. Arterial pH that exceeds 7.45 indicates alkalemia, generated by bicarbonate retention, hyperventilation relative to metabolic need, or both. Arterial pH less than 7.35 indicates acidemia, caused by metabolic or renal depletion of bicarbonate, hypoventilation relative to metabolic need, or both. Venous blood varies in composition depending on the delivery/consumption characteristics of the locally sampled tissue bed. Central venous gases, representing admixture from tissues throughout the body, generally have a PCO$_2$ that is 4 to 8 mm Hg higher and a pH that is 0.05 to 0.10 units lower than arterial gases. Occasionally, these arteriovenous discrepancies can be much wider, and in such cases, the venous value may more accurately reflect the acid-base status of vital tissue beds.

INTERPRETATION

The ABG reports the pH and allows the clinician to determine the relative contributions of respiratory and metabolic sources. Because compensation is never complete, the dominant underlying mechanism—acidosis or alkalosis—is suggested by the pH. Does a blood gas demonstrating a PaCO$_2$ of 32 mm Hg and an of 16 mEq/L indicate respiratory alkalosis with renal compensation, or metabolic acidosis with respiratory compensation? A major clue is provided by the pH—acidemia would suggest that the fundamental problem is metabolic. Failure of the PaCO$_2$ to fall to the expected level would suggest a superimposed problem with ventilatory drive or ventilatory pump. Classically, “Winters’ formula” (following) predicts the respiratory compensation for an uncomplicated metabolic acidosis. Intensive care unit (ICU) clinicians must be alert for “triple” acid-base disorders in which two metabolic derangements with opposing influences on pH are in play. The anion gap calculation usually provides the key to appropriate interpretation.

Chronicity of the process can be judged by comparing the observed values of pH, bicarbonate, and base excess with those expected for acute hypercapnia or hypocapnia (see following). To place such information into proper perspective for diagnosis and management decisions, the clinician must take account of the clinical backdrop and examine the serum electrolytes and albumin for evidence of renal insufficiency, renal tubular dysfunction, and an anion gap that indicates the presence of such noncarbonic (metabolic) acids as lactate, ketoacids, and salicylate.

The Anion Gap

The anion gap is the difference between the serum sodium concentration and the sum of chloride and bicarbonate ions. Normally, the gap is 13 mEq or less—a reflection of the sulfates, phosphates, and other unmeasured negatively charged ions that correspond to kidney-excreted “mineral” acids. Because of the anionic nature of serum proteins, the calculated gap should be adjusted by 2 to 2.5 mEq/L for each g/dL of hypoalbuminemia. Another useful bedside computation is the “Δ/Δ,” the ratio of the anion gap to the bicarbonate gap. As lactic acidosis develops, the anion gap increases relatively more than the HCO$_3^-$ falls because HCO$_3^-$ has a wider volume of distribution. The ratio varies but averages approximately 1.5 in moderate lactic acidosis—less if the acuity is extreme and more as the severity worsens. Values less than 1 should prompt consideration of another source of H$^+$ excess, whereas a value greater than 2 suggests a concurrent metabolic alkalosis.

Rules for Compensation
As already noted, primary metabolic disturbances are incompletely compensated by changes in ventilation, and primary respiratory disturbances are partially offset by renal excretion or retention of bicarbonate. Knowledge of these expected compensations allows a judgment to be made regarding the nature and chronicity of the underlying processes.

**Respiratory Compensation for Metabolic Disturbances**

A useful equation for predicting the PaCO$_2$ during a primary metabolic disturbance is as follows:

*Metabolic Acidosis (Winters’ Formula):*

\[
\text{Expected PaCO}_2 = 1.54 \times [\text{HCO}_3^-] + 8.36 \text{mm Hg}
\]

*Metabolic Alkalosis:*

\[
\text{Expected PaCO}_2 = 0.7 \times [\text{HCO}_3^-] + 20 \text{mm Hg}
\]

For example, if a measured \([\text{HCO}_3^-]\) were 16, the expected compensation would be PaCO$_2 = 1.5 \times \text{[HCO}_3^-]\ + 8 = 24 + 8 = 32 \text{ mm Hg}$. Note that the pH would be less than 7.40, however, because the \([\text{HCO}_3^-] / (0.03 \times \text{PaCO}_2)\) ratio is \(16/(0.03 \times 32) = 16/0.96 = 16.7 < 20\). If measured \([\text{HCO}_3^-]\) were 36 mEq/L, the expected compensation would be PaCO$_2 = 0.7 \times \text{[HCO}_3^-]\ + 20 \text{ mm Hg} = 0.7 \times (36) + 20 = 25.2 + 20 = 45 \text{ mm Hg}.

**Metabolic Adjustments for Primary Respiratory Disturbances**

The kidney requires time to compensate for a sustained respiratory disturbance and adjusts more successfully to respiratory alkalosis than to respiratory acidosis. The following are simple rules for the \([\text{HCO}_3^-]\) expected in the acute and chronic settings.

*Acute Rule:* \([\text{HCO}_3^-]\) rises 1 mEq/L for each 10 mm Hg rise in PaCO$_2$ above 40 mm Hg and falls 2 mEq/L for each 10 mm Hg fall in PaCO$_2$ below 40 mm Hg.

*Chronic Rule:* \([\text{HCO}_3^-]\) rises 4 mEq/L for each 10 mm Hg rise in PaCO$_2$ above 40 mm Hg and falls 3 mEq/L for each 10 mm Hg fall in PaCO$_2$ below 40 mm Hg.

**Algorithm for Evaluating Blood Gas Data**

A systematic approach to blood gas evaluation incorporates the elements of the foregoing discussion. The first priority is to verify the technical validity of the sample—errors in sampling, sample processing, analysis, and transcription occur commonly. (Is the sample characteristic of a venous rather than the intended arterial specimen? Are the pH, PaCO$_2$, and \([\text{HCO}_3^-]\) internally consistent? Does the \([\text{HCO}_3^-]\) correlate with the \([\text{HCO}_3^-]\) directly analyzed from venous blood? Is the PaO$_2$ reported physically possible given the FiO$_2$ administered?)

Although there is no best method for interpreting a technically valid report, one logical approach has the following steps:

1. Look at the arterial pH: A pH outside the normal range defines acidemia (<7.35) or alkalemia (>7.45).
2. Look at the PaCO$_2$: If PaCO$_2$ is less than 35 mm Hg, the patient has primary or compensatory respiratory alkalosis. If PaCO$_2$ is more than 45 mm Hg, the patient has primary or compensatory respiratory acidosis.
3. Look at the \([\text{HCO}_3^-]\) and compute the base excess, knowing that each 10 mm Hg rise in PaCO$_2$ generates 1
mEq/L of bicarbonate via protein buffers and each fall of 10 mm Hg reduces \([\text{HCO}_3^-]\) by a similar amount. Compute the difference between the adjusted \([\text{HCO}_3^-]\) and 24 as the base excess or deficit. If the base excess exceeds 2, the patient has a metabolic alkalotic disturbance—primary or secondary. A deficit exceeding 2 indicates a primary or compensatory metabolic acidosis.

1. Look at the serum electrolyte and albumin concentrations. Calculate the albumin-adjusted anion gap and the \(\Delta/\Delta\) for clues to the nature of metabolic derangements (see Chapter 12). A metabolic acidosis unaccompanied by an anion gap usually means renal tubular dysfunction, excessive administration of chloride in the form of “normal” saline, or gastrointestinal loss of bicarbonate.

5. Consider the clinical setting and make a judgment regarding the nature of the primary acid-base disturbance. As a general but not infallible rule, pH will be driven in the direction dictated by the primary variable—an alkalemia in conjunction with a low PaCO\(_2\) is at least partially driven by a respiratory mechanism; acidemia in conjunction with a low PaCO\(_2\) suggests that the respiratory alkalosis is compensatory.

6. Look for evidence of a mixed disorder (as opposed to a simple but compensated disturbance) by calculating the expected value of the variable not involved in the primary disturbance, using the rules given earlier. Acid-base disorders can be single (e.g., respiratory acidosis, with or without compensation), double (e.g., respiratory acidosis, metabolic alkalosis), or even triple (e.g., respiratory acidosis, metabolic alkalosis, and metabolic acidosis)—as indicated by an anion gap together with CO\(_2\) retention and a disproportionately elevated \([\text{HCO}_3^-]\). Review the clinical data and electrolytes for clues to the clinical significance of the acid-base data.

**Monitoring Oxygenation**

The human eye is not adept at detecting or quantifying arterial hypoxemia. Although intimately linked, O\(_2\) saturation and tension (partial pressure) provide complementary clinical data. PaO\(_2\) reflects the maximal tension driving O\(_2\) to the tissues, whereas saturation reflects O\(_2\) content per gram of hemoglobin. Reflectance oximetry is used when a fiberoptic catheter continuously tracks oxygen saturation in the central venous, pulmonary arterial, or systemic arterial bloodstreams. Multichannel fiberoptic chemiluminescent catheter systems for continuously monitoring PaO\(_2\), PaCO\(_2\), and arterial pH have been introduced into clinical practice several times over the past two decades for tracking either rapidly changing clinical events or progress after a clinical intervention (e.g., ventilator adjustment). Unfortunately, this potentially useful technology is not presently available for clinical use.

**Estimating Arterial Oxygen Concentration and Adequacy**

**Arterial Pulse Oximetry**

Transcutaneous photometric oximetry is useful for monitoring patients with marginal or fluctuating oxygen exchange. For patients supported by mechanical ventilation, transcutaneous oximetry continuously measures SaO\(_2\), enabling rapid adjustment of FiO\(_2\), mean airway pressure, and positive end-expiratory pressure (PEEP) and warning of arterial desaturation during weaning, sleeping, or changes of body position. As a general rule, trends in oximetry values are of greater significance than the absolute value of saturation, at least over the clinical saturation range usually encountered.

**Technical Issues**

Lightweight probes direct filtered light of several specific wavelengths onto the surface of the digit, nasal
bridge, or ear lobe. The relative absorption of these spectrophotometric beams as they pass through the tissue (which differs for O$_2$ saturated and desaturated blood) is converted into the appropriate saturation value by computer-stored algorithms. Phasic variations separate the incoming arterial component from venous and background absorption. Pulse oximetry probes do not require tissue heating because phasic changes in blood volume and optical density cue the instrument to the arterial component of the blood contained in the vascular bed. Most units also display pulse rate, and many display a simulated arterial waveform or some other visual indicator of pulse intensity. A tracing whose waveform baseline varies dramatically with ventilation strongly suggests variation of stroke output synchronous with the respiratory cycle—a finding typical for relative hypovolemia during passive mechanical ventilation, gas trapping, and auto-PEEP (AP).

The pulse rate should be “correlated” to the electrocardiogram (ECG) measured rate to assess signal quality. Good correlation does not ensure accuracy, but poor correlation of the heart rate displayed on the ECG and pulse oximeter calls the reported saturation value into question. With a good pulse signal, currently available instruments are quite accurate over their upper range (i.e., saturations > 80%) but become less reliable as the patient desaturates or perfusion deteriorates. Even when accurate, pulse oximetry displays a rolling average number with a brief time lag behind the real time value. Poor perfusion and/or probe contact are the primary causes of an erroneous signal, and placement on a different digit, nose bridge, ear lobe, or forehead may improve reliability in some patients.

Potential Artifacts

Motion artifact occasionally is an important problem for patients who are not immobilized. Because detection of the “arterial” segment of the cycle depends on small phasic changes in the tissue volume, large-amplitude vibrations of other kinds that are unassociated with arterial pulsation can confuse the sampling algorithm—especially when the frequencies of the rhythmic vibration approximate the patient's own heart rate. When a patient has a rhythmic tremor (Parkinson disease, anxiety, agitation, seizures, essential tremor, shivering, etc.), tissue volumes can vary phasically in such a way as to invalidate the oximeter's output, which trends toward the default value. In the absence of any detected discrimination between the “baseline” and arterial absorption differences, many devices default to a recorded display of 85% to 88%. Rarely, when arterial perfusion is poor or venous pulsations are vigorous, the recorded value may be misleadingly depressed.

Anemia and jaundice do not routinely affect the accuracy of pulse oximetry. Pulse oximetry values tend to be misleadingly high in some deeply pigmented patients, but by no means in all. (The existing literature conflicts on this point.) Carboxyhemoglobin and methemoglobin can produce falsely high saturation values, and specific nail polishes (particularly blue, green, or black) interfere with light transmission and absorbance, as do certain blood-borne dyes, such as indocyanine green and methylene blue. These tend to artifactually reduce the O$_2$ saturation reported.

INTERPRETATION

Many practitioners do not fully understand the oxyhemoglobin dissociation relationship (Fig. 5-1) or the value and limitations of transmission oximetry. Over the clinically relevant range, the oxyhemoglobin dissociation curve is highly nonlinear, so a drop of a few percentage points in SaO$_2$ over the 95% to 100% interval reflects a much larger change in PaO$_2$ than does a similar decrement over the 80% to 85% interval. Pulse oximeters record the relative absorption of light by oxyhemoglobin and deoxyhemoglobin. Therefore, for a fixed value of viable
hemoglobin, the saturation parallels its relative O$_2$ content, but a high saturation guarantees neither total blood O$_2$ content nor the adequacy of tissue O$_2$ delivery. For example, a patient may have a “full” SaO$_2$ after inhaling a high concentration of carbon monoxide, and yet directly measuring arterial oxygen content per deciliter of blood (by co-oximetry) may demonstrate profound arterial O$_2$ depletion. Moreover, a patient in circulatory shock may maintain a perfectly normal SaO$_2$ despite serious O$_2$ privation. Cyanide blocks the uptake of oxygen by the tissues, so O$_2$ consumption is low even as arterial and mixed venous saturations are normal or increased. Arterial oxygen saturation also bears no direct relationship to the adequacy of ventilation; a patient breathing a high-inspired concentration of oxygen will maintain a nearly normal SaO$_2$ for extended periods in the face of a full respiratory arrest.

Other gas-measuring techniques (e.g., transcutaneous and transconjunctival measurements of O$_2$ and CO$_2$) have been used widely in neonatology to monitor tissue gas tensions, but traditional monitors have been generally less helpful for adults. These transcutaneous techniques require frequent calibration, excellent skin and electrode preparation to ensure gas transfer to the skin surface, and regular site changes to avoid slowly burning the warmed skin.
patch of skin they monitor. More importantly, they are profoundly affected by inadequacy of perfusion and therefore track arterial gas tensions unreliably during many critical illnesses. Alert patients tolerate conjunctival probes poorly. Newer tissue oxygen sensors appear to hold considerably more promise.

Several methods now in active development have been used largely in a research setting but show good potential for clinical monitoring of microcirculatory function during circulatory failure. These include CO₂ measurements for sublingual, buccal, and subcutaneous microcirculatory CO₂ levels, as well as absorbance, reflectance, and near infrared spectroscopy (NIRS) for measuring microcirculatory hemoglobin saturation. NIRS can probe to considerable depth and has already found clinical application in the assessment of cerebrocortical viability. Orthogonal polarization spectral (OPS) imaging and sidestream dark field technology allow microscopic visualization of the deeper lying microcirculation and the flow of red blood cells in the microcirculation. Sublingual capnography combined with OPS imaging has been used to investigate the relationship between the microcirculation and metabolic status during resuscitation. Combinations of these technologies, which look at different functional compartments of regional microcirculations, can integratively probe the distributive alterations of oxygen transport during sepsis, septic shock, and therapy that are not provided by conventional monitoring of systemic hemodynamic and oxygen-derived variables.

**O₂ Consumption**

Although theoretically valuable for assessing nutritional requirements, adequacy of oxygen delivery, or response to hemodynamic interventions, total body oxygen consumption ([V with dot above]O₂) is often difficult to measure accurately at the bedside—even in those receiving mechanical ventilation. Two primary methods are in general use: direct analysis of inspired and expired gases and the Fick method (computation of [V with dot above]O₂ from the product of cardiac output [CO] and the difference in O₂ content between samples of arterial and mixed venous blood). Neither method reflects average oxygen consumption when the patient’s metabolic rate fluctuates during data collection. For some purposes, an estimate of CO₂ production—which is considerably more convenient to obtain—may serve to answer the question of interest (see following).

**Efficiency of Oxygen Exchange**

**Computing Alveolar Oxygen Tension**

To judge the efficiency of pulmonary gas exchange, mean alveolar oxygen tension (PAO₂) must first be computed. The ideal PAO₂ is obtained from the modified alveolar gas equation:

\[
PAO_2 = PIO_2 - \left(\frac{\text{PaCO}_2}{R}\right) + \left[\left(\text{PaCO}_2 \times \text{FiO}_2 \times (1 - R)/R\right)\right]
\]

Here R is the respiratory exchange ratio and PIO₂ is the inspired oxygen tension adjusted for FiO₂ and water vapor pressure at body temperature (47 mm Hg at 37°C).

\[
PIO_2 = (\text{barometric pressure} - 47) \times \text{FiO}_2
\]

Under steady-state conditions, R normally varies from approximately 0.7 to 1.0, depending on the mix of metabolic fuels. When the same patient is monitored over time, R generally is assumed to be 0.8 or neglected entirely. Under most clinical conditions, the alveolar gas equation can be simplified to:

\[
PAO_2 = PIO_2 - (1.25 \times \text{PaCO}_2)
\]

For example, at sea level with a normally ventilated patient breathing room air:
Alveolar-Arterial Oxygen Tension Difference \( \text{P(A-a)O}_2 \)

The difference between alveolar and arterial oxygen tensions, \( \text{P(A-a)O}_2 \), takes account of alveolar \( \text{CO}_2 \) tension and therefore eliminates hypercapnia from consideration as the sole cause of hypoxemia. However, although useful, a single value of \( \text{P(A-a)O}_2 \) does not characterize the efficiency of gas exchange across all \( \text{FiO}_2 \)s—even in normal subjects. The \( \text{P(A-a)O}_2 \) in a young normal subject ranges from approximately 10 mm Hg (on room air) to approximately 100 mm Hg (on an \( \text{FiO}_2 \) of 1.0). (Breathing room air, the upper limit of normal approximates age/4 + 4 mm Hg.) Moreover, \( \text{PAO}_2 \) changes nonlinearly with respect to \( \text{FiO}_2 \) as the extent of \( [V \text{ with dot above}]/[Q \text{ with dot above}] \) mismatch increases. When the \( [V \text{ with dot above}]/[Q \text{ with dot above}] \) abnormality is severe and abnormally distributed among gas exchanging units, the \( \text{PAO}_2 \) may vary little with \( \text{FiO}_2 \) until high fractions of inspired oxygen are given (Fig. 5-2). Finally, the \( \text{P(A-a)O}_2 \) may be influenced by the fluctuations in venous oxygen content.

\[
\text{PAO}_2 = 0.21 \times (760 - 47) - (1.25 \times \text{PaCO}_2) \\
= 150 - (1.25 \times 40) \\
= 100 \text{ mm Hg}
\]

**FIGURE 5-2.** Effect of true shunt (\( Q_s/Q_t \); left) and ventilation/perfusion mismatching (right) on the relationship between arterial oxygen tension (\( \text{PaO}_2 \)) and inspired oxygen fraction (\( \text{FiO}_2 \)). Hypoxemia caused by true shunt is refractory to supplementary oxygen once the shunt fraction exceeds 30%. Similar reductions in \( \text{PaO}_2 \) caused by ventilation/perfusion mismatching respond to oxygen; however, the \( \text{FiO}_2 \) required to boost \( \text{PaO}_2 \) into an acceptable range depends on whether hypoxemia is caused by an extensive number of units with mildly abnormal ventilation/perfusion mismatching (Uniform) or by a smaller number of units with very low ventilation-to-perfusion ratios (Non-uniform).

**Venous Admixture and Shunt**

Under normal circumstances (e.g., exercise), decreases in mixed venous \( \text{O}_2 \) saturation (\( \text{SvO}_2 \)) do not cause or contribute significantly to hypoxemia. However, as ventilation/perfusion inequality or shunting develops, the \( \text{O}_2 \)
content of mixed venous blood (CvO$_2$) exerts an increasingly important effect on SaO$_2$. Measuring SvO$_2$ with a fiberoptic pulmonary arterial (Swan-Ganz) catheter enables venous admixture ($Q_s/Q_t$) to be computed with relative ease. In the steady state:

$$Q_s/Q_t = (CAO_2 - CaO_2) / (CAO_2 - CvO_2)$$

where the oxygen content of alveolar capillary blood (CAO$_2$), arterial blood (CaO$_2$), or mixed venous blood (C[v with bar above]O$_2$), expressed in mL of O$_2$ per 100 mL of blood, equal the sum:

$$[0.003 \times PO_2] + [0.0138 \times (SO_2 \times Hgb)]$$

(In the latter equation, PO$_2$ [mm Hg] and SO$_2$ [%] refer to the oxygen tension and saturation of blood at the respective sites. Hemoglobin [Hgb] is expressed in g/dL.) Like P(A-a)O$_2$, $Q_s/Q_t$ is also influenced by variations in [V with dot above]/[Q with dot above] mismatching and by fluctuations in SvO$_2$ and FiO$_2$. If $Q_s/Q_t$ is abnormally high but all alveoli are patent, calculated admixture will diminish toward the normal physiologic value (approx. 5%) as FiO$_2$ increases. Conversely, if the $Q_s/Q_t$ abnormality results entirely from blood bypassing the patent alveoli through intrapulmonary communications or through an intracardiac defect, there will be no change in $Q_s/Q_t$ as FiO$_2$ increases (“true” shunt).

**Simplified Measures of Oxygen Exchange**

Several pragmatic approaches have been taken to simplify bedside assessment of O$_2$ exchange efficiency. The first is to quantitate P(A-a)O$_2$ during the administration of pure O$_2$. After a suitable washin time (5 to 15 minutes, depending on the severity of the disease), pure shunt accounts for the entire P(A-a)O$_2$. Furthermore, if hemoglobin is fully saturated with O$_2$, dividing the P(A-a)O$_2$ by 20 approximates the shunt percentage (at FiO$_2$ = 1.0). As pure O$_2$ replaces alveolar nitrogen, some patent but poorly ventilated units may collapse—the process of “absorption atelectasis.” Moreover, because shunt percentage is affected by changes in CO and mixed venous O$_2$ saturation, these simplified measures may give a misleading impression of changes within the lung itself. Whatever its shortcomings, determining the shunt fraction is worthwhile because it alerts the clinician to consider nonparenchymal causes of hypoxemia (e.g., arteriovenous malformation, intracardiac right-to-left shunting). Furthermore, because PaO$_2$ shows little response to variations in FiO$_2$ at true shunt fractions greater than 25%, the clinician may be encouraged to reduce toxic and marginally effective concentrations of oxygen.

The PaO$_2$/FiO$_2$ (or “P/F”) ratio is a convenient and widely used bedside index of oxygen exchange that attempts to adjust for fluctuating FiO$_2$. Although simple to calculate, this ratio is affected by changes in SvO$_2$ and PEEP and does not remain equally sensitive across the entire range of FiO$_2$—especially when shunt is the major cause for admixture. Another easily calculated index of oxygen exchange properties, the PaO$_2$/PAO$_2$ (or “a/A”) ratio, offers similar advantages and disadvantages as FiO$_2$ is varied. Like the P/F ratio, it is a useful bedside index that does not require blood sampling from the central circulation but loses reliability in proportion to the degree of shunting. Furthermore, in common with all measures that calculate an “ideal” PAO$_2$, even the a/A ratio can be misleading when fluctuations occur in the primary determinants of SvO$_2$ (hemoglobin and the balance between oxygen consumption and delivery).

None of the indices discussed thus far account for changes in the functional status of the lung that result from
alterations in PEEP, AP, or other techniques for adjusting average lung volume (e.g., inverse ratio ventilation, lateral positioning, or prone positioning). If the objective is to categorize the severity of disease or to track the true O_2_ exchanging status of the lung in the face of such interventions, the P/F ratio falls short. The oxygenation index, PaO_2/(FiO_2 × mean P_AW), takes the effects of PEEP and inspiratory time fraction into account. It is often expressed as the inverse to indicate oxygenation difficulty. In this form has gained widespread popularity in neonatal and pediatric practice to track lung status but has yet to catch hold in adult critical care. Although useful, this index, too, is imperfect; mean airway pressure and FiO_2 bear complex and nonlinear relationships to PaO_2 when considered across their entire ranges.

**Monitoring Carbon Dioxide and Ventilation**

**Kinetics and Estimates of Carbon Dioxide Production**

Body stores of carbon dioxide are far greater than are those for oxygen. When breathing room air, only approximately 1.5 L of O_2 is stored (much of it in the lungs), and some of this stored O_2 remains unavailable for release until life-threatening hypoxemia is under way. Although breathing pure O_2 can fill the alveolar compartment with an additional 2 to 3 L of oxygen (a safety factor during apnea or asphyxia), these O_2 reserves are still much less than the approximately 120 L of CO_2 normally stored in body tissues. Because of limited oxygen reserves, PaO_2 and tissue PO_2 change rapidly during apnea, at a rate that is highly dependent on FiO_2.

CO_2 stores are held in several forms (dissolved, bound to protein, fixed as bicarbonate, etc.) and are distributed in compartments that differ in their volumetric capacity and ability to exchange CO_2 rapidly with the blood. Well-perfused organs constitute a small reservoir for CO_2 capable of quick turnover, skeletal muscle is a larger compartment with sluggish exchange, and bone and fat are high-capacity chambers with very slow filling and release. Practically, the existence of large CO_2 reservoirs with different capacities and time constants of filling and emptying means that equilibration to a new steady-state PaCO_2 after a step change in ventilation (assuming a constant rate of CO_2 production, [V with dot above]CO_2) takes longer than generally appreciated—especially for step reductions in alveolar ventilation (Fig. 5-3). With such a large capacity and only a modest rate of metabolic CO_2 production, the CO_2 reservoir fills rather slowly, so PaCO_2 rises only 5 to 8 mm Hg during the first minute of apnea and 3 to 6 mm Hg each minute thereafter. Depletion of this reservoir can occur at a faster rate.

Measurement of CO_2 excretion is valuable for metabolic assessment and computations of dead space ventilation. Estimates of CO_2 production are representative when the sample is collected carefully in the steady state over adequate time. The rate of CO_2 elimination is a product of minute ventilation ([V with dot above]E) and the expired fraction of CO_2 in the expelled gas. If gas collection is timed accurately and the sample is adequately mixed and analyzed, an accurate value for excreted CO_2 can be obtained. However, whether this value faithfully represents metabolic CO_2 production depends on the stability of the patient during the period of gas collection—not only with regard to [V with dot above]O_2 but also in terms of acid-base fluctuations, perfusion constancy, and ventilation status with respect to metabolic needs. During acute hyperventilation or rapidly developing metabolic acidosis, for example, the rate of CO_2 excretion overestimates the true metabolic rate until surplus body stores of CO_2 are washed out or bicarbonate stores reach equilibrium. The opposite obtains during abrupt hypoventilation or transient reduction in cardiac output.
FIGURE 5-3. Effect of step changes in ventilation on \( \text{PaCO}_2 \). After an abrupt change in ventilation, \( \text{PaCO}_2 \) either climbs (step decrease in ventilation) or descends (step increase in ventilation) toward a new plateau. Equilibration is reached more slowly after a step decrease in ventilation because the large storage reservoir for \( \text{CO}_2 \) can be filled only at the rate of \( \text{CO}_2 \) production. Elimination of \( \text{CO}_2 \) can occur more rapidly.

**Efficiency of CO\(_2\) Exchange**

The volume of \( \text{CO}_2 \) produced by the body tissues varies with metabolic rate (fever, pain, agitation, sepsis, etc.). In the mechanically ventilated patient, many vagaries of \( \text{CO}_2 \) flux can be eliminated by controlling ventilation and quieting muscle activity with deep sedation, with or without paralysis. \( \text{PaCO}_2 \) must be interpreted in conjunction with the \( \dot{V}\text{E} \). For example, the gas exchanging ability of the lung may be unimpaired even though \( \text{PaCO}_2 \) rises when reduced alveolar ventilation is the result of diminished respiratory drive or marked neuromuscular weakness. As already noted, alveolar and arterial \( \text{CO}_2 \) concentrations respond quasi-exponentially after step changes in ventilation, with a half-time to final value of approximately 3 minutes during hyperventilation but a slower half-time (16 minutes) during hypoventilation. These differing time courses should be taken into account when sampling blood gases after making ventilator adjustments.

**Dead Space and Dead Space Fraction**

**Dead Space**

The physiologic dead space \( (V_D) \) refers to the “wasted” portion of the tidal breath that fails to participate in \( \text{CO}_2 \) exchange. A breath can fail to accomplish \( \text{CO}_2 \) elimination either because fresh \( \text{(CO}_2\text{-free)} \) gas is not brought to
the alveoli or because fresh gas brought there fails to contact systemic venous blood. Thus, tidal ventilation is wasted whenever CO$_2$-laden gas recycles to the alveoli with the next tidal breath. Alternatively, a portion of the tidal volume is wasted if fresh gas distributes to inadequately perfused alveoli, so CO$_2$-poor gas is exhausted during each exhalation (Fig. 5-4). If this concept is understood, then it becomes clear why $V_D$ cannot be considered accurately as a composite of physical volumes. Nonetheless, wasted ventilation traditionally is characterized conceptually as the sum of the “anatomic” (or “series”) dead space and the “alveolar” dead space. Because the airways fill with CO$_2$-containing alveolar gas at the end of the tidal breath that is reinspired at the onset of the next, the physical volume of the airways corresponds rather closely to their contribution to wasted ventilation (the anatomic dead space)—provided mixed alveolar gas is similar in composition to the gas within a well-perfused alveolus. This is almost true for a quietly breathing normal subject, in whom the alveolar dead space (poorly perfused alveolar volume) is negligible. When the parenchyma is well aerated and well perfused, the anatomic dead space is relatively fixed at approximately 1 mL/lb of predicted body weight. Quite the opposite is true for patients with most lung diseases, in whom alveolar dead space predominates. Here, the lung is composed of well and poorly perfused units, so the mixed alveolar gas within the airways at end-exhalation has a CO$_2$ concentration lower than that of pulmonary arterial blood. Although $V_D$ may increase dramatically, the contribution of stale airway gas to total $V_D$ is much less important because less airway CO$_2$ is recycled to the alveoli.
FIGURE 5-4. Two definitions of ventilatory dead space that apply both to patients with normal and diseased lungs. Wasted ventilation of CO\textsubscript{2} (red dots) can arise from small tidal breaths (left panel) or from interrupted perfusion of well-ventilated alveoli (right panel). Tidal ventilation can be ineffective if the gas flowing to the alveolus during inspiration contains a high concentration of carbon dioxide (left). Alternatively, tidal ventilation is ineffective in eliminating CO\textsubscript{2} if fresh gas flows to poorly perfused alveoli (A as opposed to B) that cannot deliver CO\textsubscript{2} to the tidal air stream (right).

For normal subjects, dead space increases with advancing age and body size and is reduced modestly by recumbency, extended breath holding, and decelerating inspiratory flow patterns. External apparatus attached to the airway that remains unflushed by fresh gas (e.g., a face mask) may add to the series dead space, whereas tracheostomy reduces it. The supine position reduces dead space by decreasing the average size of the lung and by increasing the number of well-perfused lung units.

Numerous diseases increase $V_D$. Loss of alveolar septae and surface area for gas exchange, low-output circulatory failure, pulmonary embolism, pulmonary vasoconstriction or vascular compression, shunted CO\textsubscript{2}, and mechanical ventilation with high tidal volumes or PEEP are common mechanisms that often act in combination.

**Dead Space Fraction**

In the setting of parenchymal lung disease, dead space varies in proportion to tidal volume over a remarkably wide range. Series dead space tends to remain fixed but generally constitutes a small percentage of the total physiologic $V_D$, overwhelmed by the alveolar dead space component (including shunted CO\textsubscript{2}). Therefore, except at very small tidal volumes, the fraction of wasted ventilation ($V_D/V_T$) tends to remain relatively constant as the depth of the breath varies. The dead space fraction can be estimated from analyzed specimens of arterial blood and mixed expired (P$_{\text{E}}$CO\textsubscript{2}) gas:

$$\frac{V_D}{V_T} = \frac{(P_{\text{a}}\text{CO}_2 - P_{\text{E}}\text{CO}_2)}{P_{\text{a}}\text{CO}_2}$$

where P$_{\text{E}}$CO\textsubscript{2} is the CO\textsubscript{2} concentration in mixed expired gas. (This expression is known as the Enghoff-modified Bohr equation.) As already noted, P$_{\text{E}}$CO\textsubscript{2} can be determined on a breath-by-breath basis if exhaled volume is measured simultaneously. Alternatively, exhaled gas can be collected over a defined period.

In healthy persons, the normal $V_D/V_T$ during spontaneous breathing varies approximately from 0.35 to 0.15, depending on the factors noted earlier (position, exercise, age, tidal volume, pulmonary capillary distention, breath holding, etc.). In the setting of critical illness, however, it is not uncommon for $V_D/V_T$ to rise to values that exceed 0.7, especially in acute respiratory distress syndrome (ARDS). Indeed, increased dead space ventilation usually accounts for most of the increase in the $[V$ with dot above]$E$ requirement and CO\textsubscript{2} retention that occur in severe acute hypoxemic respiratory failure. In such cases, the ventilating alveoli function relatively normally but are fewer in number. To eliminate the CO\textsubscript{2} load and maintain PaCO\textsubscript{2}, they must be hyperventilated out of proportion to their blood flow. This calculated dead space is primarily the result of surface area loss due to the smaller numbers of functioning lung units of the ARDS “baby lung” and of shunted CO\textsubscript{2}, rather than impaired perfusion of poorly functioning lung units (Fig. 5-5).
FIGURE 5-5. Important mechanisms that contribute to dead space formation in ARDS. Left: Overventilation of small-capacity “baby” lungs needed to eliminate CO₂ production raises the $V/Q$ ratio, even though aerated lung may be normally perfused. Right: Shunted CO₂ in ARDS does not access the ventilated alveoli and thus forms part of the dead space.

In addition to pathologic processes that increase dead space, changes in $V_D/V_T$ occur during periods of hypovolemia or overdistention by high airway pressures. This phenomenon is often apparent when progressive levels of PEEP are applied to support oxygenation without proportional recruitment of well-functioning lung. Examination of the airway pressure tracing under conditions of controlled, constant inspiratory flow ventilation may demonstrate concavity or a clear point of upward inflection (positive “stress index”; see following), indicating overdistention, increased dead space formation, and escalating risk of barotrauma. Small reductions in PEEP or tidal volume may then reduce both cycling pressures and $V_D/V_T$.

**Monitoring of Exhaled Gas**

Capnography analyzes the CO₂ concentration of the expiratory airstream, plotting CO₂ concentration against time or against exhaled volume, which provides information of greater clinical utility. After anatomic dead space has been cleared, the CO₂ tension rises progressively to its maximal value at end-exhalation, a number that reflects the CO₂ tension of mixed alveolar gas. For normal subjects, the transition between phases of the capnogram is sharp, and once achieved, the alveolar plateau rises only gently. Furthermore, when ventilation and perfusion are evenly distributed, as they are in healthy subjects, end-tidal PCO₂ ($P_{ET}CO_2$) closely approximates PaCO₂. ($P_{ET}CO_2$ normally underestimates PaCO₂ by 1 to 3 mm Hg.) This difference widens when ventilation and perfusion are matched suboptimally, allowing alveolar dead space gas to dilute CO₂-rich gas from well-perfused alveoli.

When plotted against a volume axis, as opposed to the time axis, the capnogram offers data of considerable clinical value. Inspection of such tracings can yield estimates for the anatomic (Fowler) dead space, as well as
For the end-tidal and mixed expired CO\textsubscript{2} concentrations (Fig. 5-6). Knowing the barometric pressure (\(P_B\)), the mixed expired value can be expressed as a percentage of the exhaled volume, which is also immediately available from the tracing. If the \(V_T\) remains constant, the product of \(P_{\text{E}CO_2} : P_B\) ratio and \([V \text{ with dot above}]_E\) is \([V \text{ with dot above}]CO_2\), and the mixed expired CO\textsubscript{2} concentration can be used in the Enghoff-modified Bohr equation to estimate the physiologic dead space fraction.

**FIGURE 5-6. Information available from an expiratory capnogram plotting PCO\textsubscript{2} concentration against exhaled volume.** Under steady-state conditions, mixed expired CO\textsubscript{2} concentration (\(P_{\text{E}CO_2}\)), a key component of the physiologic dead space fraction and \([V \text{ with dot above}]CO_2\), is easily discerned. The slope of the alveolar plateau is a measure of ventilation heterogeneity. The Fowler dead space (DS) is a close correlate of anatomic dead space. End-tidal PCO\textsubscript{2} (\(P_{\text{ET}CO_2}\)) reflects the concentration of CO\textsubscript{2} within the alveolar units that are last to empty. Although this value may parallel PaCO\textsubscript{2} in normal individuals, it is less reliable in disease.

As with other monitoring techniques, exhaled CO\textsubscript{2} values must be interpreted cautiously. The normal capnogram is composed of an ascending portion, a plateau, a descending portion, and a baseline (Fig. 5-6). In disease, the sharp distinctions between phases of the expiratory capnogram, as well as the slopes of each segment, are blurred. Moreover, failure of the airway gas to equilibrate with gas from well-perfused alveoli invalidates \(P_{\text{ET}CO_2}\) as a reflection of PaCO\textsubscript{2}, especially as respiratory frequency fluctuates (Fig. 5-7). (For a given CO\textsubscript{2} output, the mixed expired \(P_{\text{E}CO_2}\) per cycle, however, remains valid.) In the steady state, PCO\textsubscript{2} gives a low range estimate of PaCO\textsubscript{2} in virtually all clinical circumstances, so a high \(P_{\text{ET}CO_2}\) strongly suggests hypoventilation. Abrupt changes in \(P_{\text{ET}CO_2}\) may reflect such acute processes as aspiration or pulmonary embolism if the \([V \text{ with dot above}]_E\) and breathing pattern (\(f, V_T,\) and \(I:E\) ratio) remain unchanged. Although breath-to-breath fluctuations in \(P_{\text{ET}CO_2}\) can be extreme, the trend of \(P_{\text{ET}CO_2}\) over time helps identify underlying changes in the ventilation set point and adequacy.
The capnogram also provides an excellent monitor of breathing rhythm. Close examination of the tracing contour and comparison with earlier waveforms may give helpful indications of circuit leaks, patient ventilator dysynchrony, equipment malfunctions, secretion retention, and changes in underlying pathophysiology. In evaluating the $P_{ET}CO_2$, it is essential to examine the entire capnographic tracing, not relying on digital readouts alone. Breathing pattern can be as influential as pathology, especially when gas flow is inhomogeneously distributed, as in airflow obstruction. Failure of the tracing to achieve a true plateau can occur because the sampling technique is inappropriate, exhalation is too brief, or ventilation is inhomogeneously distributed. Thus, the $P_{ET}CO_2$ may fluctuate for a variety of reasons, not all of which imply changes in lung status. The arterial to end-tidal $CO_2$ difference is minimized when perfused alveoli are recruited maximally. On this basis, the $(PaCO_2-P_{ET}CO_2)$ difference has been suggested as helpful in identifying “best PEEP” (Fig. 5-7). This technique may have value for patients in whom a clear inflection point observed on the ascending limb of the airway pressure tracing suggests recruitable volume (see following).

**FIGURE 5-7.** Effect of breath size on end-tidal $PCO_2$ ($P_{ET}CO_2$) for normal and abnormal lungs. Double-headed thin arrows indicate difference between end-tidal and arterial $PCO_2$ values for abnormal lungs (dashed line). A higher $P_{ET}CO_2$ results from longer exhalation time that follows a deep breath when $[V with dot above]/[Q with dot above]$ is abnormal. Unlike the normal setting (solid line), the $\Delta(P_{ET}CO_2 to PaCO_2)$ margin narrows substantially for the diseased lung during the more complete exhalation associated with a slower breathing frequency.

**MONITORING LUNG AND CHEST WALL MECHANICS**

**General Principles**
For cooperative ambulatory patients, respiratory mechanics—those properties of the lung and chest wall that
determine the ease of chest expansion—are best measured in the pulmonary function laboratory. However, because most patients with critical illness cannot cooperate and are often supported by a mechanical ventilator, the clinician must serve as the on-site analyst of pulmonary function.

Certain properties (e.g., compliance of the chest wall and respiratory system) can be assessed only under passive conditions; others (e.g., maximal inspiratory pressure [MIP]) require active breathing effort. The mechanical properties of the lung—a passive object—can be determined with or without active breathing effort, provided estimates of pleural pressure as well as airway pressure and flow are available. Although pleural pressure—traditionally estimated by esophageal balloon (see following)—is not measured in most patients, its potential value is high when the pressures applied across the lung are of concern (e.g., in ventilating ARDS). Finally, to separate static (e.g., compliance) from dynamic (e.g., flow resistance) variables, points of zero flow within the tidal cycle must be determined exactly; to accomplish this, the clinician may need to assure passive inflation and impose a well-timed pause of appropriate length.

**Pressure-Volume Relationships**

A good understanding of static pressure-volume (PV) relationships is fundamental to the interpretation of chest mechanics. Although this complex topic cannot be addressed thoroughly here, certain key concepts deserve mention. Because the lung is a flexible but passive structure, gas flows to and from the alveoli driven by differences between airway and alveolar pressures—no matter how they are generated. The total pressure gradient expanding the respiratory system is accounted for in two primary ways: (1) in driving gas between the airway opening and the alveolus and (2) in expanding the alveoli against the recoil forces of the lung and chest wall. The pressure required for inspiratory flow dissipates against friction while the elastic pressure that expands the respiratory system is stored temporarily in elastic tissues until dissipated primarily in driving expiratory flow.

**Normal Values for Resistance and Compliance**

For clinical purposes, the nonelastic impedance to airflow offered by friction and movement of the lung and chest wall is termed “resistance.” The elastic impedance these structures offer in opposing inflation is termed “elastance,” and its reciprocal is the more familiar term “compliance.” For a point of reference, the normal airway resistance of a healthy adult is less than 4 cm H$_2$O/L/s when breathing spontaneously and rises approximately twofold when orally intubated with a tube of standard size and length (tube diameter is always substantially less than that of the trachea). The elastances of the lungs ($E_L$) and chest wall ($E_{CW}$) add in series to determine that of the respiratory system ($E_{RS}$): $E_{RS} = E_L + E_{CW}$. Compliances add in parallel (see following). At end-expiration, the compliance values for the lung, chest wall, and integrated respiratory system of a spontaneously breathing, healthy adult patient of normal size and weight in the supine position are approximately 200, 150, and 85 mL/cm H$_2$O, respectively.

**Static Properties of the Respiratory System**

Accurate estimation of respiratory system properties cannot be accomplished in the ventilated patient using airway pressure alone unless the breathing is passive. Furthermore, what independent contributions the lung and chest wall make to the measured overall compliance require an estimate of pleural pressure. With these caveats in mind, the PV relationships measured during mechanical ventilation are informative. The relationship between pressure and volume varies markedly over the vital capacity (VC) range (Fig. 5-8). For short segments (chords), this relationship can be considered approximately linear over most regions of the PV curve. Therefore, assuming linearity, the elastic properties of the lung, chest wall, and integrated respiratory system can be described by single values for chord elastance ($\Delta P/\Delta V$) or its inverse, chord compliance ($\Delta V/\Delta P$). The tidal compliance measured at the bedside ( $V_t/[\text{Plateau} - \text{total PEEP}]$) is the chord compliance of the respiratory
system. (Chord compliance differs from tangential compliance, which is the slope at a single point on the curve.) Lung compliance is influenced by the number of open lung units available to accept the tidal volume, a point of special importance in ARDS. Furthermore, when tidal recruitment of collapsed lung units occurs over the tidal volume range, calculations of chord compliance may not characterize the elastic properties of the underlying tissue. Examination of the PV relationship indicates that chord compliance differs according to the segment over which it is computed.

**FIGURE 5-8. Normal static PV relationships of the lung, chest wall, and total respiratory system.** With no pressure applied to the airway opening, the outward recoil pressure of the chest wall at end-expiration counterbalances the inward collapsing pressure of the lung at functional residual capacity (FRC).

**Specific Compliance**
Because flow and volume are measured in absolute units (L/s and L), the same ΔP will result in a different ΔV for two lungs of identical tissue properties but different capacities (see below). For example, identical pressures drive greatly different volumes into the chest of a patient before and after pneumonectomy. Until very recently, we have had no way to measure lung capacity at the bedside, but the measurement of functional residual capacity (FRC) by gas dilution is now an option on some of the latest ventilators, allowing the estimation of the specific compliance of tissue that is accessible to air.

**Respiratory System Compliance and Elastance**
The portion of the applied airway pressure that expands the lung by a certain volume (ΔV) is the corresponding
change in transpulmonary pressure: \( P_L = (P_{alv} - P_{pl}) \), where \( P_{alv} \) = alveolar pressure and \( P_{pl} \) = pleural pressure.

The lung elastance (\( E_L = \Delta P_L / \Delta V \)) is the pressure per unit of inflation volume required to keep the lung expanded under no-flow (static) conditions. It has been customary to refer to lung compliance, the reciprocal of elastance (\( C_L = 1 / E_L = \Delta [V with dot above] / \Delta P_L \)). In similar fashion, the distensibility of the passive, relaxed chest wall is characterized by chest wall compliance (\( C_W = \Delta V / \Delta P_{pl} \)). The slope of the static inspiratory PV relationship for the total respiratory system is \( C_{RS} \) (\( C_{RS} = \Delta V / \Delta P_{alv} \)). The term “driving pressure” is applied to \( \Delta P_{alv} \), the difference between plateau pressure and total PEEP. In ventilator-derived calculations of compliance, \( \Delta V \) (normally, the tidal volume) must be measured at the endotracheal tube or expired volume must be adjusted for the volume stored during pressurized inflation in compressible circuit elements. Most modern ventilators do this automatically.

Compliance measurements obtained under passive conditions may have therapeutic and prognostic value for patients with arterial desaturation. However, regional lung mechanics vary (Fig. 5-10). In the setting of lung edema (e.g., ARDS), many lung units are collapsed or closed at FRC and reopen at various pressures as the lung distends toward total lung capacity (TLC). At the same time, other lung units (often predominating in less gravitationally dependent zones) distend to the point of overstretching. When PEEP is applied incrementally and the lung is passive, \( C_L \) and \( C_{RS} \) tend to reach their highest values for a given tidal volume when the balance of opening and overstretching is most favorable and driving pressure is least. (Chest wall properties do, however, influence the measurements made.) This zone also tends to be that associated with minimal ventilatory dead space and shunt fraction and often coincides with the zone of maximal oxygen delivery. Because of tidal recruitment, different tidal volumes are associated with different “optimal PEEP” values. Many experts believe that PEEP is best set after first fully expanding the lung—in other words, on the deflation limb, not the inflation limb of the PV loop. It is a good rule to avoid using values of end-expiratory pressure or tidal volume that depress tidal thoracic compliance—unless objective evidence of significantly improved oxygen delivery is available and safe plateau and driving pressures are not exceeded. At any one point in time, lower compliance may indicate a smaller number of open lung units or overdistention of those already open. Followed over time, serial changes in the respiratory PV curve and \( C_{RS} \) tend to reflect the nature and course of acute lung injury. Severe disease is implied when compliance falls to less than 25 mL/cm H₂O. Maximal depression of \( C_{RS} \) often requires 1 to 2 weeks to develop in the setting of acute lung injury, signifying both fewer functioning lung units and lower compliance of those that remain open. Although \( C_{RS} \) provides useful information regarding the difficulty of chest expansion, \( C_{RS} \) does not necessarily parallel underlying tissue elastance—both the size of the alveolar compartment and the relative position on the PV curve are important to consider.

Ideally, compliance is referenced to a measure of absolute lung volume, such as FRC or TLC (“specific” compliance). Furthermore, \( C_{RS} \) may differ greatly between the extremes of the VC range, even in the same individual (Fig. 5-9). Thus, most patients with hyperinflated lungs ventilated for acute exacerbations of asthma or chronic obstructive pulmonary disease (COPD) exhibit depressed \( C_{RS} \), despite normal or “supernormal” tissue distensibility and specific compliance; \( C_{RS} \) would be a better indicator of tissue elastic properties if measured in a lower volume range. As already noted, elastances add in a simple series, so \( E_{RS} = E_L + E_{CW} \). Yet, because compliances add in parallel, \( C_{RS} \) bears a more complex relationship to the individual compliances of the lung (\( C_L \)) and chest wall (\( C_W \)).
FIGURE 5-9. Computation of tidal (chord) compliance of the respiratory system. An identical tidal volume ($\Delta V$) results in quite different values for compliance ($\Delta V/\Delta$elastic pressure). In this example, tidal compliance, the inverse of the slope of the chord linking the two volumes over which tidal volume was delivered, is best in the middle third of the inspiratory curve (BC), worst in the top third of the curve (CD), and intermediate in the bottom third (AB). Arrows indicate zones of inflection (recruitment predominates) and deflection (over distention predominates).

\[ C_{rs} = \frac{C_L \times C_w}{C_w + C_L} \]

The fraction of PEEP transmitted to the pleural space depends on the relative compliances of the lungs and chest wall:

\[ \Delta P_{pl} = PEEP \times \left( \frac{C_L}{C_L + C_w} \right) \]

Chest Wall Compliance

The usual assumption that the PV characteristic of the chest wall is normal and remains linear and unchanging throughout its range is often inappropriate for critically ill patients whose chest wall distensibility may be disturbed by abdominal distention, pleural effusions, ascites, muscular tone, recent surgery, position, binders, braces, and so on (see following). Such changes in $C_w$ are very important to consider in that they dramatically influence $P_{PL}$. In turn, $P_{PL}$ influences venous return, hemodynamic data (e.g., pulmonary artery occlusion pressure, $P_{pw}$), and calculations of chest mechanics based on airway pressure (e.g., driving pressure). As already noted, an appropriate interpretation of tidal airway pressures
for the lung depends on a valid assessment of intrapleural pressure. Moreover, specific values for peak airway pressure and $C_{RS}$ have different prognostic significance, depending on whether the lung or chest wall accounts for the stiffness.

**Influence of Pleural Effusion**

The presence of a large pleural effusion alters the usual interpretation of chest mechanics. Contrary to intuition, the formation of a large pleural effusion often does not substantially reduce the measured compliance of the total respiratory system. With the chest wall and abdomen normally flexible, the lung expands into and displaces the fluid and diaphragm during the breath, causing extensive tidal recruitment. The addition of PEEP restores normal compliance of the lung and markedly reduces the tidal component of recruitment. In a sense, the fluid “uncouples” the lung from the chest wall. If the chest wall is unusually stiff, however, the linkage between the lung and the chest wall tightens, and pleural fluid formation then does impede tidal recruitment and lung expansion. Clearly, in the presence of an effusion, attempts to identify “best PEEP” are not reliably made by measuring respiratory system compliance, and the stress index may be quite misleading (see following).

**Clinical Utility of the Pressure-Volume Curve**

In the acutely injured lung of ARDS, virtually all lung units may sustain initial damage, but not all are equally compromised or mechanically equivalent. In severe cases, perhaps only 25% to 30% of alveoli remain patent, the others being atelectatic or occluded by lung edema, cellular infiltrate, or inflammatory debris. Moreover, the mechanical properties of the lung differ in dependent and non-dependent regions. For a supine patient, atelectasis, flooding and infiltration predominate in dorsal sectors, where lung units tend to collapse under the influence of regionally increased pleural pressure and the weight of the overlying lung. This proclivity is greatest at FRC, when transalveolar pressure is least. In this surfactant-deficient lung, there are tendencies for persisting collapse of dependent alveoli and/or tidal reopening and recollapse of lung units in the middle and dependent zones. The latter process subjects injured tissue to damaging shear forces when high inflation pressures are used. According to current thinking, both persisting collapse of inflamed tissue and the tidal collapse cycle must be avoided. To aid in healing, some knowledgeable investigators believe that the objective is to “open the lung and keep it open” without causing overdistention (see Chapter 24).

Many alveoli—especially those in nondependent zones—remain open and relatively compliant but are subject to overdistention by high peak tidal pressures. These regional differences give rise to an inspiratory PV curve with poor compliance in its initial and terminal segments. Defining the PV relationship may help guide the ventilator settings needed to avoid the damaging effects of both tidal collapse and alveolar overdistention. The PV curve is a composite of information from myriad lung units, and its contours are shaped by the relative numbers of open (recruited) units and the proportions of units at various stages of distension (see Chapters 9 and 24). In the setting of ARDS, it appears that recruitment occurs to some degree throughout the TLC range. Therefore, the inflation limb of the PV curve is shaped by two phenomena occurring simultaneously—opening of lung units being recruited and distention or overfilling of those already open. Although not everyone agrees, most investigators of ventilator-induced lung injury currently believe that sufficient end-expiratory alveolar pressure (total PEEP [PEEP<sub>TOT</sub>], see Chapter 9) should be maintained to surpass the lower inflection zone ($P_{\text{flex}}$ region) of the inspiratory PV curve when high end-inspiratory (plateau) pressures are in use. Although approximately 12 to 15 cm H$_2$O generally suffices to approximate $P_{\text{flex}}$ in the early stage of ARDS, the PEEP requirement will vary with body size, stage, and severity of lung injury as well as with chest wall compliance. At the same time, peak tidal alveolar pressure should not encroach on the upper deflection zone that signals widespread alveolar overdistention. (A few sustained inflations to high static pressure may be necessary to open the lung and set decremental PEEP in the initial stages of ARDS, and periodic “recruiting breaths” may be needed when very small tidal volumes are used.) The pressure needed to fully recruit the recruitable lung units may be as low as 25
P.105

cm H\textsubscript{2}O in some individuals and as high as 60 cm H\textsubscript{2}O in others, influenced heavily by the type and duration of lung injury and by chest wall characteristics. It should be noted that PEEP is an expiratory pressure and that less pressure is needed to keep lung units open than to open them once they close. (This difference gives rise to hysteresis of the inspiratory-expiratory PV loop.) It follows that setting PEEP is more rationally done by first opening the lung to TLC (opening as many units as possible) and then dropping PEEP from a high value to a lower one that prevents widespread collapse (see Chapters 8 and 24).

**Construction of the Static PV Curve**

No simple rules for choosing optimal PEEP apply to all patients because the compliance characteristics of their lungs and chest walls differ so radically. Consequently, there is no completely satisfactory alternative to defining the entire PV curve, even though this is not always feasible or even safe to undertake. Disconnection of the ventilator may cause a marked drop in mean and end-expiratory transalveolar pressures that can cause hypoxemia, bradycardia, arrhythmia, and/or flooding of the airway with edema fluid. For this reason, many physicians forgo PV curve measurement entirely in their most severely ill patients or elect to use methods whereby the patient remains connected to the ventilator as PEEP and/or tidal volume are varied.

Traditionally, the inspiratory PV curve is constructed in a passive patient by briefly disconnecting the patient from the ventilator and attaching an oxygen-filled, 2- to 3-L “super syringe” to the airway opening. After establishing a uniform inflation “history,” airway pressure is followed as serial 100-mL volumes are injected until TLC is reached. Static pressures are recorded 2 to 3 seconds after injection of each increment. The entire process is completed within 60 to 90 seconds. The $P_{\text{flex}}$ and the upper deflection zones used to guide PEEP and applied pressure or tidal volume selections may be defined carefully by using smaller injection steps in the early and late phases. In recent years, a slow inflation at constant flow (approx. 2 L/min) delivered by the ventilator has been used as a simplified (and even automated) means of obtaining essentially the same information. Unfortunately, reliance on the airway pressure tracing (a synthesis of information from all lung zones) may be misleading, as regional lung PV relationships with radically different local contours may be imbedded within it (Fig. 5-10).
FIGURE 5-10. Regional PV relationships. As the lung fills at a constant rate, the rising total lung pressure bears an apparently linear relationship to volume that actually is a composite of steadily recruiting and overdistending lung units.

Construction of an expiratory PV curve has more theoretical appeal as a means for setting PEEP, as its contours are more directly influenced by the events of expiratory collapse that PEEP is intended to prevent. The construction of such a curve is more painstaking, however, as it currently requires stopping expired flow and measurement of the corresponding alveolar pressure in a series of steps (see Chapters 9 and 24). Assuming that tidal volume has already been selected, tracking tidal compliance during decrements of PEEP (proceeding from higher to lower values) has logical appeal for setting PEEP’s optimal value. Following this reasoning, the least PEEP associated with best tidal compliance and preserved oxygenation is the preferred value. Recruitment and decremental PEEP setting rationale and method are discussed more fully in Chapters 9 and 24.

Driving Pressure

The tidal compliance has long been used as an indicator with which to identify the ‘best peep’ to use with a fixed tidal volume. In a rearrangement of the elements of the compliance-defining equation, the ratio of tidal volume to measured compliance (numerically the difference between two static pressures, $P_{\text{plat}}$ and $PEEP_{\text{TOT}}$) has been called the ‘driving pressure, DP’ (Fig. 5-11). Because tidal compliance is determined primarily by the number (rather than the stiffness) of open lung units, this easily measured indicator effectively references tidal volume to the aeratable capacity of the lung. It therefore would appear to be a good candidate to track pulmonary stress. In fact, DP may be the best measurable ventilation predictor of mortality risk in ARDS. Although influenced by chest wall stiffness, lung heterogeneity, pleural effusions, unmeasured AP, and
nonmechanical cofactors of ventilator-induced lung injury (VILI), the DP appears currently to be a good compromise variable to target for a lung protective ventilation strategy (see Chapters 8 and 24).

**FIGURE 5-11. Computation of compliance and resistance of the respiratory system under passive conditions during constant inspiratory flow ([V with dot above]_{\text{in}}).** An end-inspiratory pause is applied to hold the inspired tidal volume before exhalation is begun. Tidal compliance is the quotient of tidal volume and the difference between static plateau pressure (P\text{S}) (equivalent to alveolar pressure, P\text{alv}) and PEEP\text{TOT}. In this example, no AP is present. The difference between peak dynamic pressure (P\text{D}) and plateau pressures, divided by [V with dot above]_{\text{in}}, equals maximum inspiratory resistance. The difference between P\text{D} and the pressure at which flow first becomes zero after the pause is applied (P_{ZF}) reflects the least resistance pressure because it excludes stress relaxation, ventilation redistribution (pendelluft), and viscoelastic pressures. Expiratory resistance requires measurement or calculation of alveolar pressure (referenced to PEEP, \Delta) and the corresponding flow it produces (V with dot above)_{\text{ex}}. Finally, the slope of the airway pressure tracing at the end of inspiration obtained under constant flow conditions reflects elastance of the respiratory system (1/C\text{RS}). PEEP, positive end-expiratory pressure.

**Imaging of Function and Structural Heterogeneity—the Future**

To this point in the history of mechanical ventilation, the primary database from which monitored information regarding mechanics derives has been limited to global measures of pressure and flow sampled from the airway opening. Such information mixes together contributions from mechanically different lung zones as well as the chest wall. Yet it is now understood that the diseased lung—whether obstructed or acutely injured—is composed of heterogeneous subunits whose behaviors and risk susceptibilities vary considerably from site to site. Measuring transpulmonary pressure using the esophageal balloon catheter is a useful and logical refinement,
but still incomplete. At sites inside the lung where open and closed units interface with each other, regional stress focusing can amplify the local effects of any given transpulmonary pressure. Poised to be introduced to the clinical practice are several methodologies designed to monitor regional anatomy and function and thereby help regulate therapy and modify risk. Foremost among these are EIT and pulmonary ultrasound. Experimental data demonstrate that the distribution and dynamic behaviors of gas flow, diaphragm, and lung pathology can be determined. Surveillance for developing pneumothorax, pleural effusion, consolidation, and tidal recruitment is only one of their potential applications. Although little clinical experience has yet been accumulated, it seems clear from an expanding base of experimental and observational studies that these “real-time imaging” methodologies have the potential to elevate respiratory monitoring of the critically ill onto a new plane of management better aligned with our understanding of underlying pathophysiology and treatment goals.

Calculation of $C_{RS}$ and $R_{AW}$ During Mechanical Ventilation

**Inspiratory Resistance and Static Compliance**

All ventilators monitor external airway pressure ($P_{AW}$). When the ventilator expands the chest of a passive subject, inspiratory $P_{AW}$ furnishes the entire power accomplishing ventilation. Because the PV relationships of the lung and chest wall are approximately linear over the tidal volume range and because the increment in $P_{AW}$ necessary to drive gas flow is nearly unchanging under constant flow conditions from zero PEEP, the corresponding $P_{AW}$ waveform resembles a trapezoid, a shape composed of a triangle of tidal elastic pressure and a parallelogram of resistive pressure (Fig. 5-11).

**Absolute Lung Volume, Specific Resistance, and Specific Compliance**

As already noted, the pressures and flows that determine resistance and compliance are measured in absolute numbers “cm H$_2$O” and “L/s.” But a moment's reflection alerts us to the powerful effect that capacity to receive air has on the calculated numbers for compliance and resistance. For example, pressure of 10 cm H$_2$O would drive a huge flow into a healthy elephant, but a tiny flow into a healthy mouse. Moreover, a high value for resistance could reflect the fewer bronchial channels for airflow, rather than hold any information related to their diameters. A change in lung compliance could result not only from a position shift along the PV relationship (e.g., hyperinflation) or from an alteration of tissue elastic properties (e.g., the development of lung fibrosis) but also from a variation in the aeratable capacity of the lung (e.g., pneumonectomy) or the development of consolidation (e.g., pneumonia). Changes in absolute lung volume—now possible to measure with gas dilution built into some ventilators—could tell us more regarding the underlying condition of the lung and about the events changes in pathology (related to recruitment and resistance) than possible without referencing FRC.

**Role of Dynamics**

Although it is customary to characterize the risk for injury to the respiratory system by its static “plateau” pressure after a sustained pause, a growing body of literature indicates that static pressures seriously underestimate the maximal stresses to which some tissues are subjected within the heterogeneous lung and shows that the rate at which elastic forces expand should not be ignored. The pattern of flow delivery (mean flow velocity and waveform)—not simply the transpulmonary pressure and the ventilating frequency—may be of vital relevance to ventilator-induced lung injury (Chapters 8 and 24). During expansion, some pressure dissipates within the airways, while another fraction of unrecovered (unstored) pressure reshapes the tissues to their static configuration (viscoelastance). Some indication of the latter is offered by the difference between the pressure at which flow first ends after end-inspiratory circuit occlusion (zero flow) and the plateau pressure (see Fig. 5-11).
In today’s clinical practice, data regarding inspiratory resistance and compliance characteristics of the respiratory system continue to be estimated during volume-cycled, constant flow ventilation using $P_{AW}$ alone. It should be emphasized, however, that calculations of $C_{RS}$ and resistance from $P_{AW}$ should be made only when inflation is passive. (During active effort, $P_{AW}$ must be referenced to esophageal pressure to make the relevant calculations for the lung.) Both chest wall stiffness and muscular effort may cause the airway pressure to be seriously misleading regarding the lung stress (gauged by the difference between static airway and intrapleural pressures) (Fig. 5-12). When gas is prevented from exiting the lung at the end of tidal inspiration, $P_{AW}$ falls quickly to a plateau value. If this end-inspiratory “stop flow,” “plateau,” or “peak static” ($P_S$) pressure is referenced to end-expiratory alveolar pressure ($PEEP_{TOT}$), their difference (the driving pressure) determines the component of end-inspiratory pressure necessary to overcome the elastic forces of inflating the chest with the delivered tidal volume. $PEEP_{TOT}$ is the sum of applied PEEP and AP. When tidal volume (adjusted for gas compression) is divided by ($P_S - PEEP_{TOT}$), effective compliance ($C_{eff}$) can be computed as follows:

$$C_{eff} = \frac{V_T}{(P_S - PEEP_{TOT})}$$

where $V_{Tc}$ is the corrected $V_T$.

The maximal pressure achieved just before the end of gas delivery (the peak dynamic pressure, $P_D$) is the total system pressure required to push gas to the alveolar level at the selected flow rate and to expand the lungs and chest wall by the full $V_T$. The difference between $P_D$ and $P_S$ quantifies the gradient driving gas flow and overcoming tissue resistance, a difference that varies with the resistance of the patient and endotracheal tube as
well as with the inspiratory gas flow setting. Under these conditions of passive ventilation and constant inspiratory flow, the ratio of \( (P_D - P_S)/[V \text{ with dot above}]_{\text{end-insp}} \) is the airway resistance \( (R_{AW}) \). When corrected for the compression volume of the external circuit, the ratio of delivered volume to \( (P_D - \text{PEEP}_{\text{TOT}}) \) reflects the overall difficulty of chest expansion, if \( V_T \) and inspiratory flow settings do not change and inflation occurs passively. This index had been termed the “dynamic characteristic” (DC):

\[
\text{DC} = \frac{V_T}{(P_D - \text{PEEP}_{\text{TOT}})}
\]

Because \( P_D \) is influenced by both the frictional and elastic properties of the thorax, it serves as a simple yet valuable indicator of bronchodilator response under passive conditions, again provided that flow rate and \( V_T \) remain unchanged. During controlled inflation with constant “square” wave inspiratory flow and stable airway resistance \( (R_{AW}) \), the slope of the inspiratory pressure ramp should reflect \( E_{RS} \) (Fig. 5-11). However, estimates of \( E_{RS} \) made by this technique (and those by the method described previously) are inappropriately low, unless AP is taken into account. When there is autoPEEP at the onset of inspiration, the relevant pressure for chest expansion is \( (P_S - \text{PEEP}_{\text{TOT}}) \), not \( (P_S - \text{PEEP}) \).

**Stress Index**

Noticeable curvature of the inspiratory pressure tracing during passive inflation with constant flow suggests that disproportionate recruitment (concave to the time axis) or disproportionate overdistention (convex to the time axis) is taking place during the tidal cycle. From the standpoint of lung protection, both are undesirable. During constant flow, the relationship between pressure and time can be expressed: \( P_{AW} \propto (t^s + [R_{in} \text{ flow} + \text{PEEP}_{\text{TOT}}]) \), where \( P_{AW} \) is airway pressure, \( t \) is inspiratory time since inflation onset, \( R_{in} \) is inspiratory resistance, and \( s \) is the shaping coefficient or stress index. When \( s = 1.0 \), the contour is linear, and when it is significantly less than or greater than 1, the stress index suggests undesirable degrees of tidal recruitment or overdistention, respectively (Fig. 5-13). Modern ventilators can automatically fit a smoothed curve to the inspiratory \( P_{AW} \) profile, calculate the stress index, and display “s” as a monitored parameter.

Although this is a quite attractive option, the clinical utility of doing so has not yet been established.
FIGURE 5-13. Concept of the “stress index.” The slope of the airway pressure during passive inflation with constant flow (“square wave,” ACV) may suggest extensive intratidal recruitment (if the curve shaping exponent b [fit to the curve $P_{RS} = a t^b + c$] is <1.0, left) or extensive overdistention (if >1.0, right). When plateau pressure is high, the former suggests that additional PEEP should be considered, whereas the latter suggests that a reducing tidal volume, PEEP, or both are prudent. Even a perfect $b = 1.0$ may hide regional problems of either type.

**Expiratory Resistance**

For the same average flow rate, expiratory resistance routinely exceeds inspiratory resistance, even in the normal airway. This discrepancy can be much larger in the clinical setting, especially when the patient is connected to a mechanical ventilator. This expiratory resistance arises in the endotracheal tube and exhalation valve as well as in the increased expiratory resistance of the native airway. The resistance across the exhalation valve and external tubing can be monitored easily by recording airway pressure and flow in the external airway. Total expiratory resistance, the quotient of expiratory flow and the difference between alveolar and airway opening pressures (or critical closing pressure if expiration is flow limited), is difficult to measure directly. However, it often can be estimated from the knowledge of expiratory flow just before an occlusion of the airway opening and the “stop-flow” pressure (which estimates alveolar pressure). Alternatively, if the time constant of tidal exhalation can be measured under passive conditions, expiratory resistance is the quotient of the time constant and respiratory system compliance.

Expiratory resistance has important consequences, giving rise to AP, neuromuscular reflexes, dyspnea, and differences between mean airway and mean alveolar pressures. Average expiratory flow and expiratory resistance increase as $[\dot{V}]_E$ rises and expiratory time shortens, reducing the time available for expiration and boosting average expiratory flow. Except when resistance and $[\dot{V}]_E$ are normal, the patient must contend with the effects of expiratory resistance by allowing dynamic hyperinflation or by increasing...
expiratory muscle pressure. For these reasons, certain ventilator manufacturers have developed techniques to offset the expiratory resistance of the endotracheal tube and circuitry.

**Endotracheal Tube Resistance**

The endotracheal tube often contributes greatly to $R_{AW}$. Depending on the nature, length, diameter, patency, and angulation of the endotracheal tube, the resistive properties of the external airway may dominate computed values for $R_{AW}$. Marked flow dependence of resistance also may be demonstrated in certain patients, a phenomenon usually attributed to turbulence developing in a narrow or partially occluded tube. If endogenous bronchial resistance is the variable of interest, $P_{AW}$ ideally should be sensed at or beyond the carinal tip of the endotracheal tube. This can be accomplished with an intraluminal catheter or by using a tube specially designed for measuring pressures at this site (e.g., tubes designed for jet ventilation or tracheal gas insufflation). Some modern ventilators estimate tube resistance, allowing for that component in their digital readouts of calculated number. Values for $C_{RS}$ (computed under static conditions) remain valid, whatever the resistances of the endotracheal tube or airway may be.

**Auto-PEEP (Intrinsic PEEP) Effects**

**Definitions of Auto-PEEP, Intrinsic PEEP, and Total PEEP**

Considerable confusion has arisen regarding the terms “auto-PEEP” and “intrinsic PEEP.” PEEP is the pressure applied to the airway by the clinician.

This is also termed “extrinsic PEEP” by some authors. The pressure measured when all airflow is stopped is equivalent to average alveolar pressure and is termed “total PEEP.” AP is the difference between PEEP$_{TOT}$ and PEEP, that is, that component of PEEP$_{TOT}$ attributable to dynamic hyperinflation. The prefix “auto” derives from the Greek term meaning “self.” Different authors use the term *intrinsic PEEP* as a synonym for PEEP$_{TOT}$, and others use it as a synonym for AP. The latter usage allows specific designation of clinician-set (extrinsic) PEEP and dynamic hyperinflation-generated (intrinsic) PEEP without ambiguity. For clarity, we use the terms PEEP (rather than extrinsic PEEP), AP (rather than intrinsic PEEP), and PEEP$_{TOT}$ throughout this book.

**FIGURE 5-14.** Simultaneous tracings of airway pressure ($P_{AW}$) and airflow during controlled volume-cycled ventilation with constant inspiratory flow in a patient with airflow obstruction. $P_D$, $P_Z$, and $P_S$ represent end-inspiratory airway pressures during dynamic conditions, at the point of flow cessation, and after complete equilibration among all alveolar and airway pressures, respectively. Alveolar pressure can be estimated by the stop-flow technique in midexpiration or at end-exhalation ($AP_1$). AP also can be estimated under dynamic
conditions as the airway pressure above the set PEEP value that is needed to counterbalance elastic recoil and stop expiratory airflow (AP₂).

FIGURE 5-15. Three forms of AP. AP can exist without dynamic hyperinflation (left) when vigorous expiratory muscle contraction persists to the end of expiration. Under the conditions of passive inflation, however, AP does imply dynamic hyperinflation—either without (middle) or with (right) expiratory flow limitation. The response to exogenous PEEP is influenced greatly by the form of AP encountered.

**Variants of Auto-PEEP**

The need for high levels of ventilation may cause hyperinflation when insufficient time elapses between inflation cycles to reestablish the equilibrium (resting) position of the respiratory system, especially in the presence of increased airway resistance and a lengthy exhalation time constant (Fig. 5-14). Consequently, when a mechanical ventilator powers inflation, alveolar pressure (\(P_{\text{alv}}\)) remains continuously positive through both phases of the respiratory cycle, and airflow does not cease at end-exhalation.

AP does not necessarily indicate dynamic hyperinflation, unless expiration occurs passively (Fig. 5-15). Even under passive conditions, the extent of dynamic hyperinflation that results from

AP is a function of respiratory system compliance. During spontaneous breathing efforts, expiratory muscle activity can raise end-expiratory alveolar pressure, sometimes preventing any hyperinflation at all. AP is also not synonymous with airflow obstruction but, rather, can occur anytime that \([V \text{ with dot above }]_E\) is high enough and/or the combination of frequency and \(f \cdot E\) ratio leaves insufficient expiratory time—even for normal subjects. Moreover, AP varies markedly from one site to another within the obstructed lung, tending to be greatest in the dependent lung regions. AP can change with variations of body position.

Although deliberate distention of the lungs by dynamic hyperinflation can be used intentionally in patients with refractory hypoxemia (e.g., APRV), AP usually occurs inadvertently, often with adverse consequences for hemodynamics, respiratory muscle function, and lung mechanics. Barotrauma is an obvious (but fortunately uncommon) risk of serious hyperinflation. Unlike restrictive lung disease, the flexible lungs of obstructive lung disease allow normal transmission of alveolar pressure to the pleural space. Thus, the hemodynamic consequences of the AP effect may be more severe than those incurred by PEEP of a similar level applied to a non-compliant respiratory system. Immediately after intubation, CO tends to drop as the AP impedes venous return during passive inflation. With some exceptions, hypotension occurs routinely after intubating a patient with serious airflow obstruction. This adverse effect of AP is particularly important to keep in mind during cardiopulmonary resuscitation, when gas trapping secondary to ill-advised vigorous ventilation further
compromises marginally adequate blood flow.

AP also adds to the work of breathing, presenting an increased threshold load to inspiration, impairing the strength of the inspiratory muscles, and depressing the effective triggering sensitivity of the ventilator. For cases in which expiration is flow limited during tidal breathing, the addition of low levels of exogenous PEEP (less than the original AP level) effectively replaces AP and therefore improves subject comfort and the work of breathing, without increasing lung volume or peak cycling pressure. Substitution of PEEP for AP also may improve the distribution of ventilation marginally. At the bedside, PEEP$_{TOT}$ can be quantified by occluding the expiratory port of the ventilator at the end of the period allowed for exhalation between mechanical breaths. As already noted, the AP component is the difference between this measured occlusion pressure and the PEEP value set by the clinician.

Variability of Auto-PEEP

Regional Gas Trapping

AP varies widely throughout a lung composed of individual units with varying time constants. Because pleural pressure follows a gravitational gradient, transpulmonary pressure and alveolar dimensions are least and the tendency for airway closure is greatest in the most dependent regions. Therefore, even if the time constants were otherwise perfectly uniform throughout the lung, there would be a tendency for units in dependent areas to trap more gas than those located above them. This happens with greater frequency when PEEP is not applied. The gas trapped behind completely closed airways exerts a pressure that cannot be measured at the airway opening. In other words, it is common to have extensive gas trapping without a measured AP that reflects its magnitude. Many morbidly obese patients undergo such regional gas trapping in as they move from upright to recumbent positions, contributing to their dyspnea when supine. This occurs even in the absence of lung pathology.

Vulnerability to Changes in Minute Ventilation

Minute ventilation is a powerful determinant of AP; in fact, in a uniform lung characterized by a single time constant, variations in frequency or tidal volume that do not change the minute ventilation have little effect on the observed AP. On the other hand, relatively small changes in $\dot{V}_E$ can dramatically change the extent of gas trapping in such a single-compartment system. In practice, the diseased lungs of exacerbated COPD and asthma patients deflate in a pattern that is better typified as biexponential or multiexponential. For these patients, end-expiratory flows from the slowest compartments are so small that increasing the cycling frequency (and increasing the minute ventilation) may have less effect on gas trapping than raising tidal volume to achieve the same rise in $\dot{V}_E$.

Alterations in Resistance and Compliance

For the same minute ventilation, variations in retained secretions, bronchospasm, apparatus resistance, tissue edema, body position, and muscle tone alter the deflation time constant and the extent of gas trapping encountered at an unchanging $\dot{V}_E$. Partially for this reason, simple maneuvers such as suctioning the airway or changing the patient from the reclining to the upright position can make a dramatic difference in the level of comfort.

Methods for Determining Auto-PEEP

The presence of AP should be suspected whenever detectable flow persists to the very end of tidal expiration (Table 5-1). Such flow at times may be audible using a stethoscope positioned over the trachea. AP (if not
dynamic hyperinflation) is certain if wheezing persists to the very end of the expiratory cycle. This flow can be transduced and displayed graphically on the bedside monitor. However, the magnitude of end-expiratory flow does not correlate with the magnitude of AP, whether comparing patients to one another or observing the same patient over time. End-expiratory flow of a given amount, for example, may result from widespread severe obstruction or from more moderate obstruction confined to a smaller subpopulation of alveoli. Moreover, very high levels of regional hyperinflation and AP can lurk behind airways that have been sealed completely by mucous plugs (with collateral ventilation). Others may open during inspiration but seal before end-expiration is reached, preventing all further discharge of their trapped gas.

Because AP varies on a breath-by-breath basis during spontaneous breathing, it cannot be quantified precisely unless exhalation is passive and the depth and duration of all breaths are equivalent—conditions that only rarely occur when making spontaneous breathing efforts. Once passive conditions are established, an estimate of AP can be determined (or its effects monitored) by a variety of methods. All these methods are approximations, and all are somewhat lower than the highest values existing within the lung. Two methods are based on the principle of counterbalancing AP, either by end-expiratory airway occlusion or by a measured dynamic airway pressure (protoinspiratory counterbalancing, or zero flow method) (Fig. 5-14). Alternatively, the AP effect can be characterized by directly measuring the change in end-inspiratory plateau (peak alveolar) pressure with a constant tidal volume and inspiratory time. Finally, the excess (trapped) gas volume that exits during an extended deflation interval reflects the corresponding end-expiratory pressure during tidal breaths. Two of the most important effects of AP—on hemodynamics and work of breathing—are mediated by pleural pressure, which can be assessed directly by measuring esophageal pressure (see following).

<table>
<thead>
<tr>
<th>Table 5-1. Clinical Methods for Determining Auto-PEEP</th>
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<td>End-expiratory port occlusion</td>
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<td>Pressure needed to initiate inspiratory flow</td>
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<td>End-inspiratory plateau pressure drop during VCV ventilation after frequency abruptly reduced</td>
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<td>Esophageal pressure decline prior to inflation onset (spontaneous breathing)</td>
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<td>PEEP substitution</td>
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<td>Trapped gas release</td>
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**End-Expiratory Port Occlusion**

For accuracy, occlusion must occur just before the subsequent ventilator-delivered breath and continue for 1.5 to 2.0 seconds. Such timing of occlusion is easiest to achieve during controlled ventilation at modest breathing rates (<20/min) and can be approximated manually or, when the patient is totally passive, automated by modern ventilators that apply a transient expiratory pause. Because gas trapping may occur in airways close early in expiration and do not communicate with the airway opening at end-expiration, end-expiratory port occlusion may underestimate their pressures and the extent of associated hyperinflation.

**Pressure Needed to Start Inflation**

During passive inflation, inspiratory flow does not begin until the expiratory pressure within the units with the least AP is counterbalanced by an offsetting proximal airway pressure. If flow and airway pressure signals are perfectly synchronous, AP is the airway pressure at the time of zero flow. This estimate for AP is usually a bit
less than that given by port occlusion.

**End-Inspiratory Plateau Pressure During Volume-Cycled Ventilation**

As already noted, alveolar pressures behind occluded airways can be elevated, even if AP measured at the airway opening is low. End-inspiratory plateau pressure is the sum of PEEP, AP, and the quotient of $V_T/C_{RS}$.

Therefore, when tidal volume and PEEP are accounted for and unchanging (as during volume assist control), plateau pressure reflects the degree of dynamic hyperinflation of all lung units more faithfully than does direct measurement of AP itself, which gives an average of the AP values from only those units that remain in communication with the airway opening. For similar reasons, change in plateau pressure that occurs after a prolonged expiration or a variation in a machine setting more reliably index changes in hyperinflation than does direct AP estimation. Assuming passive inflation with a constant tidal volume and applied PEEP, the easiest clinical method at rapid breathing frequencies is to first measure the plateau pressure at the clinically relevant frequency and to then resume the clinical pattern (without the measurement pause) for five or more breaths. Next, the frequency is slowed to less than 5 breaths/min, waiting 15 seconds before reapplying the end-inspiratory pause. The difference in pause pressures estimates the original AP.

**PEEP Substitution**

When PEEP is added downstream from the site of critical flow limitation, end-expiratory alveolar pressure rises only modestly until the original level of AP is surpassed, at which point the alveolar and airway pressures rise together. As PEEP is substituted for AP, end-expiratory flow slows or stops completely, and audible flow or wheezing ceases before end-expiration. In flow-controlled, volume-cycled ventilation, plateau pressure changes little until the original level of average AP is approached. In pressure-controlled ventilation, tidal volume may crest at its maximum as PEEP approaches the critical level and AP disappears. Although imprecise and unreliable in (rather unusual) patients with severe airflow obstruction who lack tidal flow limitation, this pragmatic technique lends itself well for both passive and actively breathing patients.

**Release of Trapped Gas**

A measurement of the *extra* gas released (in excess of the routine tidal volume) in the first exhalation after a sudden and dramatic slowing of ventilatory frequency (to 2 breaths or less/min) estimates the amount of the trapped gas ($V_{TR}$) that can be expelled. (Gas that remains trapped behind completely closed airways is not recorded.) If compliance of the respiratory system ($C_{RS}$) is known, AP can be low-end estimated as $V_{TR}/C_{RS}$. 
Flow Limitation

Flow limitation during tidal breathing is a marker of airflow severity and of the collapsibility of the airways. Flow limitation during forceful breathing is what lends reproducibility to the FEV$_1$ measurement in the pulmonary function testing laboratory. If a ventilated patient is flow limited during tidal breathing, (s)he cannot respond to a need for more ventilation without suffering further hyperinflation. Flow-limited patients usually show an abrupt L-shaped transition to sharply reduced expiratory flows, which then slowly approach the zero-flow baseline in a linear rather than exponential trajectory. Display of flow-volume loops is now an option available on many modern ventilators. One simple way to evaluate flow limitation is to increase pleural pressure selectively during expiration (e.g., by mimicking the action of the expiratory muscles by manually compressing the abdomen firmly and steadily during expiration), and observing whether volume-referenced flows improve. Failure to do so may indicate benefit from incrementing external PEEP.

Esophageal Pressure Monitoring

Estimation of intrapleural pressure by an esophageal catheter holds the potential to improve clinical decision making. The flaccid esophagus of the lower mediastinum shares the pleural pressure that surrounds it, and that local pressure can be estimated by a low-volume balloon mounted over a catheter of the same approximate diameter as a feeding tube (Fig. 5-16).

Esophageal pressure measurement enables a local estimate of pleural pressure and therefore allows calculation of the pressure across the lung during passive or active breathing. Pleural pressure determination also permits estimation of pressure changes across the chest wall when spontaneous efforts
are silenced. It stands to reason that with the aid of $P_{es}$ measurements, local end-inspiratory lung stress, compliance, and the transpulmonary driving pressure can be more accurately estimated than when using plateau pressure alone (Fig. 5-17). Transition of transpulmonary pressure from negative ($P_{aw} - P_{es} < 0$) to positive ($P_{aw} - P_{es} > 0$) indicates opening of local alveoli and has been used successfully in ARDS to set “open lung” PEEP. Other uses are to detect tidal opening and closure, maximal tidal transpulmonary pressure, and driving pressure across the lung whether or not there is spontaneous effort. The $P_{es}$ accurately reflects the pleural pressure of its local environment and tracks changes throughout the aerated lung space quite well. $P_{es}$ can be used to detect AP during spontaneous breathing efforts. Finally, transdiaphragmatic pressure ($P_{di}$), the difference between $P_{es}$ and the balloon catheter-measured gastric pressure, is generated theoretically by a single inspiratory muscle (the diaphragm) and can be used to quantify its effective contractile force. This viable application, as well as measurement of transvascular intrathoracic pressure, is seldom encountered in clinical practice.

**FIGURE 5-17.** Transpulmonary pressures, the difference between airway and esophageal pressures ($P_{es}$), distend the lung at end expiration (left) and end-inspiration (right). Lung volume expands from functional residual capacity (FRC) by the tidal volume ($V_T$) added during tidal inflation. The transpulmonary driving pressure ($DP_{TP}$) is the difference between the end-inspiratory and end expiratory values.

**Practical Points**
The thin esophageal catheter (approx. 2-mm diameter) is relatively comfortable, is simple to insert, and poses little risk of esophageal perforation. Appropriate placement is achieved by first inflating the 10-cm-
long balloon with approximately 1 mL of air and passing it into the stomach. The catheter is carefully withdrawn 10 cm beyond the position where negative pressure deflections are initially observed during spontaneous inspiratory efforts. The balloon's final position within the lower third of the esophagus is tested by occluding the airway and measuring the simultaneous deflections in $P_{AW}$ and $P_{es}$. Because no significant change of transpulmonary pressure can occur without a change in lung volume, good balloon position is indicated by nearly identical deflections of esophageal and airway pressures during an occluded spontaneous breath. If the patient is passive, fluctuations of pleural pressure during the temporary airway occlusion are made by brief and repeated abdominal compressions. As a rule, $P_{es}$ offers the best estimation of average pleural pressure in the fully upright position. Although the absolute value of the average pressure that surrounds the lung cannot be gauged accurately from such a local sampling, fluctuations of average intrathoracic pressure can be estimated acceptably well by an occlusion-tested balloon catheter in any position. It has been suggested that fluctuations in central venous pressure can serve similar purposes, but the damped vascular pressure tracing yields a low-range estimate of effort. Such underestimation occurs because venous return tends to rise as intrathoracic pressure falls; conversely, venous return declines when intrathoracic pressure rises.

Certain commercially available systems are designed to sample esophageal pressure in conjunction with airway pressure and flow, outputting primary and derived mechanics data of clinical interest (e.g., resistance, compliance, and several indices of inspiratory effort during active breathing conditions). Esophageal pressure enables estimation of force generation during all patient-initiated breaths (spontaneous or machine-assisted) and allows partitioning of transthoracic pressure into its lung and chest wall components during passive inflation. During patient efforts, $P_{es}$ is a valuable aid in detecting asynchrony. Esophageal pressure magnitude and trend has been reported useful in tracking patient tolerance during weaning. The intrapleural pressure provided by the $P_{es}$ tracing also permits calculation of lung compliance and airway resistance during spontaneous breathing. Furthermore, $P_{es}$ aids in interpreting pulmonary artery and wedge pressures under conditions of vigorous hyperpnea or elevated alveolar pressure (PEEP, AP). The $P_{es}$ can be used to compute the work of breathing across the lung and external circuitry or to calculate the product of developed pressure and the duration of inspiratory effort (the pressure-time product). Finally, as already noted, knowing the transpulmonary lung stress applied by a given plateau pressure may help to prevent ventilator-induced lung injury by guiding PEEP selection and estimating transpulmonary stress and driving pressures during active breathing (see Chapters 8 and 24).

Abdominal Pressure Measurement

In most patients with acute respiratory failure, increased chest wall stiffness usually occurs because of an increase of intra-abdominal pressure (IAP). In fact, chest wall elastance (the inverse of compliance) relates more or less linearly to IAP, and approximately one fourth of all patients admitted to the ICU have an abnormally high IAP value. Although pressures measured within any flaccid hollow viscus can be used, the bladder pressure in the horizontal position has become the de facto standard because of its ease of measurement and established correlation with directly measured values. Assuming passive conditions, the IAP measured at end expiration in healthy subjects is approximately 0 cm H$_2$O during spontaneous breathing and somewhat higher in mechanically ventilated patients on PEEP without obvious abdominal pathology (6 to 12 cm H$_2$O). The transmission fraction of abdominal pressure to the pleural space under passive conditions is approximately 50% of the increment above approximately 7 cm H$_2$O. Although bladder pressure does not equate to esophageal pressure, it serves several main functions: (1) high values indicate cephalad displacement of the diaphragm, reduced inflation compliance,
and increased work of breathing; (2) a high IAP predicts that $P_{es}$ is also high, on occasion prompting direct $P_{es}$ measurement; and (3) a very high IAP may result in life-threatening impairment of perfusion to the kidney, gut, and other abdominal organs. Values of IAP that rise to exceed 20 cm H$_2$O are a cause for concern regarding the abdominal compartment syndrome (see Chapter 35). It should be noted that although values of abdominal pressure greater than 20 cm H$_2$O are sometimes seen chronically, without detectable problems, a rapidly rising IAP in the correct clinical setting and accompanied by a developing anion gap acidosis or otherwise unexplained deterioration of urinary output is a cause for immediate surgical consultation.

**Value of Continuously Monitoring $P_{aw}$ and Flow**

**The Flow Tracing**

Most modern ventilators offer the option of displaying waveforms of both airway pressure and airflow. When used in conjunction with a simultaneously recorded airway pressure, the flow tracing is an invaluable aid in determining a number of parameters of clinical interest. A glance at the flow tracing usually is sufficient to determine the inspiratory mode of the ventilator, and when used in conjunction with airway pressure, it detects patient-ventilator asynchrony. Clusters of asynchronous breaths detected from airway pressure and flow tracings have been linked to adverse clinical outcomes (Chapter 8). The tracing of flow not only times each breath but also provides crucial data that allow computation of tidal volume, minute ventilation, frequency to tidal volume ratio (rapid shallow breathing index), and breathing pattern variability (see Chapter 10). Flow must be known to compute airway resistance and the work of breathing, as well as to detect (but not quantify) AP without airway occlusion. A smoothly linear, biphasic flow profile, rather than a unexponential one, may give a clear indication of expiratory flow limitation. A rippling inspiratory flow tracing indicates secretion retention within the central airways. The “zero flow” points of the airway and esophageal pressure tracings define the dynamic mechanical limits of the respiratory cycle, which are required in computations of mouth occlusion pressure ($P_{0.1}$, see following), minimum airway resistance, and AP. The flow tracing also is helpful when adjusting the inspiratory period during time-cycled, pressure-preset forms of ventilation (e.g., pressure-controlled ventilation) to maximize inspiratory tidal volume while avoiding unintended end-inspiratory pauses and/or excessive AP.

**The Airway Pressure Tracing**

A continuous tracing of $P_{aw}$ provides useful information, much of which is commonly neglected at the bedside (Figs. 5-11 and 5-18).
FIGURE 5-18. Tracings of airway and esophageal pressure during asynchronous assist/control ventilation with constant inspiratory flow. Variations in contour and peak cycling pressure characterize asynchrony between the respiratory rhythms of the patient and ventilator.

Apart from enabling estimation of $R_{AW}$ and $C_{RS}$, the waveform of inspiratory airway pressure traced during a controlled machine cycle provides graphic evidence of the inflation work performed by the ventilator at the particular combination of tidal volume and flow settings in use. When inflation occurs passively during constant flow, the area under the pressure-time curve is proportionate to the work performed by the machine to inflate the chest, and the pressure measured halfway through inspiration ($\Delta OV0440;$) is the work per liter of ventilation under those conditions. When average flow and tidal volume are matched to spontaneous values, $\Delta OV0440;$ is a good estimate of the pressure needed to ventilate the patient during a conversion to pressure-supported ventilation.

The shape of the airway pressure tracing also should be examined (Fig. 5-18). Using constant inspiratory flow, concavity of the airway pressure ramp reflects patient effort during triggered cycles. An upward inflection of the terminal portion of the inspiratory airway pressure tracing (concavity) during passive inflation suggests that the combination of end-expiratory pressure and tidal volume chosen generates pressures that risk overdistention and barotrauma. Conversely, marked convexity of the $P_{AW}$ tracing during constant flow indicates that inflation is becoming easier as the breath proceeds. Such a profile can be seen when volume is alternately recruited and derecruited during the breathing cycle, when AP is present (requiring a range of counterbalancing pressures before units with different AP values are brought “online” for inspiration), or when resistance is highly volume dependent (Fig. 5-13). These shaping characteristics are reflected in the stress index (see above). Cycle-to-cycle variations in the peak dynamic pressure of spontaneously triggered, machine-aided breaths suggest that the durations of inspiratory effort and flow delivery are not well matched or synchronous (Fig. 5-18).

In deeply sedated patients, pressurization of the airway can elicit an involuntary “reverse trigger” that can be identified on the airway pressure tracing as an interruption of the otherwise smooth profile. Although its cause and clinical significance are unknown, this relatively common phenomenon seems likely to result from a diaphragmatic reflex evoked by relatively abrupt or rapid thoracic expansion.
FIGURE 5-19. Relationship of mean airway pressure to mean alveolar pressure. In an airway in which inspiratory (R_{in}) and expiratory (R_{ex}) resistive pressure losses are equivalent, the mean pressure averaged over the entire ventilatory cycle should be equivalent at every point along the path, including airway opening and alveolus. When R_{ex} exceeds R_{in}, mean alveolar pressure exceeds mean airway opening pressure; when R_{in} exceeds R_{ex}, mean airway opening pressure exceeds mean alveolar pressure.

Mean Airway Pressure

Under passive conditions, mean alveolar pressure and its only measurable analog, mean airway pressure (mP_{AW}), relate intimately to the forces that drive ventilation and hold the lung distended. When the nonelastic pressures dissipated in inspiration and expiration are identical, the airway pressure averaged over the entire ventilatory cycle should be the same everywhere—including the alveolus (Fig. 5-19). This mean pressure is the average pressure that distends the alveolus and passive chest wall and therefore correlates with alveolar size and
recruitment as well as with mean intrapleural pressure. Mean alveolar pressure also is the average pressure available to drive expiratory flow, which is indexed by minute ventilation. It follows that mean airway (mean alveolar) pressure, when measured without patient effort, correlates directly with arterial oxygenation in the setting of pulmonary edema and lung injury, with back pressure to venous return (and consequently with CO and peripheral edema), as well as with minute ventilation.

Mean airway pressure can be raised by increasing $V_{\dot{E}}$, by raising end-expiratory pressure, or by extending the inspiratory time fraction (see Chapters 9 and 24). To avoid serious and unanticipated problems in the passive patient, mean airway pressure is a crucial variable to monitor when the clinician changes minute ventilation or alters the mode of ventilation, breathing pattern, or PEEP setting.

Although the relationship between $mP_{AW}$ and $mP_{alv}$ is a close one, these pressures are not identical. The actual relationship can be expressed mathematically as

$$mP_{alv} = mP_{AW} + V_{\dot{E}} (R_{ex} - R_{in})$$

where $R_{ex} - R_{in}$ is the calculated difference between expiratory and inspiratory resistances. For reasons already discussed, this pressure difference generally tends to be positive and may be strikingly so in the setting of severe airflow obstruction with high ventilatory requirements or high frequency or inverse ratio ventilation.

### MONITORING BREATHING EFFORT

#### Oxygen Consumption of the Respiratory System

The oxygen consumed by the ventilatory pump ($[V with dot above]O_{2R}$) estimates respiratory muscular effort at its most basic level: cellular metabolism. In theory, $[V with dot above]O_{2R}$ accounts for all factors that tax the respiratory muscles; in other words, the external workload ($W$) and the efficiency ($e$) of the conversion between cellular energy and useful work ($[V with dot above]O_{2R} = W/e$). Two patients with different chest configurations, patterns of muscle activation, or degrees of coordination between the muscles of inspiration and expiration may perform identical external work ($W$) but consume vastly different amounts of $O_{2}$ in the process. Because $[V with dot above]O_{2R}$ cannot be measured directly, total body oxygen consumption ($[V with dot above]O_{2}$) is tracked as ventilatory stresses are imposed or relieved, perturbing the respiratory system. Unfortunately, $[V with dot above]O_{2}$ is difficult to measure in unstable patients. Thus, other measures of respiratory muscle effort usually are sought.

#### Direct Measures of External Mechanical Output

##### External Work of Breathing

Mechanical work is accomplished when a pressure gradient ($P$) moves the lung or relaxed chest wall (passive structures) through a volume change. At volumes ($V$) above relaxed FRC, pressure resulting from a flow ($V$) dissipates against frictional and elastic forces in the following way:

$$P = R_{AW} \left( \dot{V} \right) + V/C_{RS}$$

Average developed pressure ($\bar{P}$) for the tidal inflation ($V_T$) can be approximated as follows:

$$\bar{P} = R_{AW} \left( V_T / t_i \right) + V_T / 2C_{RS} + \text{auto-PEEP}$$

It is numerically equivalent to the work per liter of ventilation. (Work per tidal breath $[W_0]$ can be quantified as the
product of $&OV0440;$ and $V_T$. Thus, if $R_{AW}$, $C_{RS}$, $t_i$, and $V_T$ are known for the spontaneously breathing subject, the external work rate for inspiration can be computed easily. (Exhalation normally proceeds passively, dissipating elastic energy stored during the inspiratory half cycle.) Such computations also serve to conveniently estimate the pressure support level needed to achieve most ventilatory needs. When the ventilator performs the entire workload for a passive patient, total inflation pressure ($P$) is simply $P_{AW}$. (When inflation is achieved with a constant-flow waveform, it is then approximated by the inflation pressure at midcycle.) However, no exertion must occur during inflation and, to be relevant to unsupported natural breathing, $V_T$ and peak flow rate must approximate the spontaneous values. With pressures and volumes expressed in the customary way, a convenient work unit is the joule (or watt-second), approximately $10 \text{ cm } H_2O \times 1 \text{ L}$ (equivalent to $1 \text{ kg } m = 10 \text{ J}$). Total inspiratory mechanical work per minute is the product of $P$ and minute ventilation or of $W_b$ and $f$, the breathing frequency. Machine work represents energy delivered to the lung per breath, and when multiplied by breathing frequency, the ventilating power. Power has been proposed as a primary if not proximate cause of VILI (see Chapter 8).

**Influence of Auto-PEEP on Spontaneous Work of Breathing**

AP imposes a threshold load on inspiration in the sense that the patient must supply a pressure sufficient to counterbalance AP before central airway pressure falls low enough to trigger the ventilator or initiate a pressure-supported breath. The threshold load imposed by AP effectively reduces the triggering sensitivity of the machine to a value equal to the sum of AP and the set trigger sensitivity value. When expiration is flow limited during tidal breathing, low levels of continuous positive airway pressure (CPAP) or PEEP can help restore triggering sensitivity and reduce the work of breathing (see earlier). Moreover, during pressure-supported ventilation, PEEP that counterbalances AP leaves a greater proportion of the inspiratory pressure available to power inflation, often resulting in an increased tidal volume for the same value of pressure support. Although PEEP also tends to improve the distribution of ventilation, additional PEEP should not be used if it causes the peak dynamic cycling pressure to rise significantly.

**Work Measurements**

**Spontaneous Breathing Cycles**

An esophageal balloon is required to directly measure work during spontaneous, machine-assisted, or pressure-supported breathing cycles. Fluctuations in $P_{es}$ reflect patient efforts to overcome the impedance of the lung and external circuit. (Clues to the work done against the external apparatus can be gained by examining the $P_{AW}$ tracing.) Inspiratory inflections of the $P_{AW}$ waveform quantify the pressure needed to suck gas through the inspiratory circuitry to the point of pressure measurement. To include the resistance of the endotracheal tube, $P_{AW}$ must be sampled between the tube tip and the carina, a site at which much deeper pressure fluctuations may be seen during inspiration (*Fig. 5-20*). The resistance of standard endotracheal tubes often exceeds $10 \text{ cm } H_2O/L/s$ and is commonly offset during inspiration by pressure support.
FIGURE 5-20. Pressure tracings at the proximal and distal ends of the endotracheal tube during spontaneous breathing. External recordings do not reflect exertion against the endotracheal tube (left). The application of pressure support may overcome endotracheal tube resistance during the inspiratory phase but does nothing to offset the expiratory resistance imposed by the endotracheal tube.

Machine-Assisted Breathing Cycles

Volume-Limited Machine Cycles

It is often assumed that patient work becomes negligible during patient-initiated but machine-assisted breathing cycles. Indeed, the ventilator is fully capable of performing the entire work of breathing if the patient were to cease effort immediately after triggering inspiration. So long as the airway pressure tracing rises above the PEEP baseline, it is giving at least some help to the patient. However, relaxation does not occur abruptly once the machine cycle begins; instead, patient effort continues in direct proportion to the intensity of respiratory drive. When the ventilation requirement or sense of dyspnea is high (e.g., when the ventilator is poorly adjusted with respect to sensitivity, peak inspiratory flow rate, inspiratory duration, or tidal volume), exertion levels may approach those of unsupported breathing. Interestingly, resistance and compliance do not influence the work of breathing during triggered cycles, provided the machine fully satisfies the patient's peak inspiratory flow demand (approx. $4 \times \dot{V}$). However, if the patient's flow demand exceeds the delivery rate, the patient works against the resistance of the endotracheal tube and ventilator circuitry as well as against the innate impedance characteristics of the chest. Clues to patient exertion during triggered machine cycles of flow controlled, volume cycled ventilation are provided by the airway pressure tracing, as already described. Peak dynamic pressure itself may not be much different from expected, inasmuch as inspiratory effort slackens near the end of inflation.

Pressure-Supported Cycles

During pressure-supported cycles, inspiratory airway pressure rises to a plateau maintained nearly constant by the machine at the preset level. Therefore, machine work is variable, and patient effort can be gauged easily and
directly only from a $P_{es}$ tracing.

**Pressure-Time Product**

Isometric components of muscle tension that consume oxygen without contributing to volume change fail to register as externally measured work, accounting in large part for the lack of agreement between force generation and $W_b$. A pressure-time product (PTP = $P_{isometric} \times \Delta t$) parallels effort and $\dot{V}O_2$ more closely than $W_b$ because it includes the isometric component of muscle pressure and is less influenced by the afterload to contraction. When average inspiratory pressure ($P_{isometric}$, as computed earlier) is referenced to the maximal isometric pressure that can be generated at FRC ($P_{max}$) and inspiratory time ($t_i$) is expressed as a fraction of total cycle length ($t_{tot}$), a useful effort index is derived:

$$\text{Pressure} \times \text{time index (PTI)} = \frac{P_{isometric}}{P_{max}} \times \frac{t_i}{t_{tot}}$$

Values of PTI that exceed 0.15 identify highly stressful breathing workloads that may not be sustainable.

**MONITORING VENTILATORY DRIVE AND BREATHING PATTERN**

**Importance of Assessing Ventilatory Drive**

Remarkably little attention has been paid to drive measurement during critical illness. Heightened ventilatory drive increases work expenditure during triggered machine cycles and often signals pain, sepsis, and important perturbations of the cardiopulmonary system. During machine-assisted breathing cycles, ventilatory drive plays a more important role in determining the energy expenditure of the patient than does any indicator of ventilatory mechanics—if the flow delivered by the machine exceeds the patient's flow demand. Derangements in ventilatory drive also furnish clues regarding the ability of the patient to wean from ventilator support. Clinical studies demonstrate that patients who fail to wean from mechanical ventilation often have elevated drives to breathe and limited abilities of drive to respond to the increases in ventilatory loads (e.g., increased PaCO$_2$).

**Ventilatory Drive Indices**

Several methods can be used to index drive. When respiratory mechanics and strength reserves are normal, minute ventilation directly parallels the output of the ventilatory control center. Unfortunately, such preconditions are seldom met in the clinical setting. Minute ventilation can be viewed as the product of mean inspiratory flow rate (the quotient of tidal volume and inspiratory time, $\dot{V}_T/t_i$) and the inspiratory time fraction or duty cycle ($t_i/t_{tot}$):

$$V_e = \frac{\dot{V}_T}{t_i} \times \frac{t_i}{t_{tot}}$$

Both components yield useful and largely ignored clinical information. Mean inspiratory flow ($\dot{V}_T/t_i$) provides another potential index of drive but also depends on the mechanical properties of the ventilatory system. The airway pressure generated against an airway surreptitiously occluded 100 ms after the onset of inspiratory effort (the $P_{0.1}$) is measured before the occlusion is recognized consciously, so the corresponding outflow from the respiratory center is representative of the unimpeded cycles that preceded it. As an isometric measurement, the $P_{0.1}$ is influenced by muscle strength and lung volume but does not depend on respiratory mechanics. Several modern ventilators display this helpful $P_{0.1}$ index, which is obtained by delaying the opening of their expiratory valve.

**Breathing Pattern, Frequency, and Duty Cycle**

**Rapid Shallow Breathing and the f/V$_T$ Ratio**
The breathing pattern also offers valuable information. When muscular strength is limited, patients tend to meet $[V_{dot}]_E$ requirements by increasing frequency ($f$) without raising $V_T$. Although smaller breaths require less effort, the cost of rapid, shallow breathing may be increased dead space ventilation and the need for a higher $[V_{dot}]_E$ to eliminate CO$_2$. Thus, although work per breath ($W_b$) is controlled by limiting tidal volume, total work (the product of $f$ and $W_b$) per minute tends to increase when $f$ exceeds some optimal value. A very high and continuously rising frequency (to rates >30 breaths/min) is generally accepted as a sign of ventilatory muscle decompensation and impending fatigue. It should be noted, however, that some patients increase $f$ to a stable value greater than 35 breaths/min and remain compensated, especially when $[V_{dot}]_E$ rises proportionally to the rise in breathing frequency.

In recent years, considerable attention has focused on the $f/V_T$ ratio, a simply computed bedside index that seems to indicate the ability or inability of mechanically ventilated patients to breathe without mechanical assistance. Discontinuation of ventilator support is likely to prove successful if ($f/V_T$) does not exceed approximately 100 breaths/min/L within the first minute of a brief trial of fully spontaneous breathing. The $f/V_T$ will tend to rise in anyone as minute ventilation increases, particularly if respiratory system compliance is reduced (see Chapter 10, Weaning). Although hardly infallible, this simple index clearly does have clinical utility.

As the ventilatory muscles fatigue, the duty cycle ($t_i/t_{tot}$), the fraction of each breathing cycle spent in inspiration, also changes. When there is a breathing stress, the $t_i/t_{tot}$ of spontaneous breathing normally increases approximately from 0.35 to a value of 0.40 to 0.50. (“Inspiratory time” may be fixed by chosen values of inspiratory flow rate and tidal volume during constant flow mechanical ventilation.) At the limits of compensation, the $t_i/t_{tot}$ fails to increase with further stress and may actually decline.

At times of maximal effort, noteworthy alterations may be observed in the pattern of activation and coordination of the ventilatory muscle groups. Although normally passive, expiratory muscles may be called into play whenever the inspiratory muscles face a burden that is stressful in relation to their capability (e.g., during expiratory airflow obstruction, when high levels of PEEP or CPAP are used, when the patient is anxious, when machine-controlled inspiratory duration is excessive, and at high levels of $[V_{dot}]_E$). Visible use of the accessory muscles, especially the sternocleidomastoid group, may also signal the approach to the limits of ventilatory compensation.

**Synchrony and Coordination of the Respiratory Muscles**

Two indices once believed to always indicate diaphragmatic dysfunction or fatigue—asynchrony between the peak excursions of chest and abdominal compartments and paradoxical inward movement of the abdomen on inspiration—often reflect the normal response of a compensated system to stress. Asynchrony between the excursions of rib cage and abdomen may be a stage in the development of fullblown abdominal paradox. **Respiratory alternans**, another reported pattern of fatigue in which muscles of the chest cage and diaphragm alternate primary responsibility for achieving ventilation, is observed much less commonly than is abdominal paradox.

**MONITORING STRENGTH AND MUSCLE RESERVE (ENDURANCE)**

The ability of a patient to sustain independent breathing must not be judged on the basis of any absolute value for workload but rather on workload interpreted against the background of muscular strength and endurance, perhaps best indicated by the observed trends in distress or breathing pattern.
Strength Measures

The two measures of respiratory muscle strength most commonly used in the clinical setting are the VC and the MIP generated against an occluded airway. Maximal activation of the respiratory musculature requires intense voluntary effort. Therefore, without full patient cooperation, it is questionable that any measure of strength can reflect the full capability for pressure development.

Vital Capacity

In cooperative patients, VC tends to be well preserved relative to MIP for two primary reasons. First, the PV relationship of the thorax is convex to the volume axis, so the small applied pressures achieve relatively large volume changes. Second, whereas many seriously ill patients can generate brief spikes of inspiratory pressure, few can sustain inspiratory effort long enough to achieve the plateau of their volume curve. VC should be generally measured upright rather than supine because certain conditions—diaphragmatic paralysis, for example, may demonstrate a positional reduction of more than 30% (see Chapter 25). Routine measurements of VC involve a single forceful effort from residual volume to TLC (or the converse). However, many weak patients fail to sustain inspiratory effort long enough to achieve their potential maximum. Others simply refuse or cannot fully cooperate with the testing. Thus, for critically ill patients, the VC has proven to be a disappointing and unreliable measure of strength. During mechanical ventilation, cough stimulation during CPAP may elicit an involuntary deep breath that approximates inspiratory capacity—a useful indicator of breathing reserve. A one-way valve can be used to achieve a “stacked VC,” even when patients do not cooperate fully with testing.

Maximal Inspiratory Pressure

The MIP (sometimes erroneously referred to as “maximum inspiratory force”) is an isometric pressure optimally measured in a totally occluded airway after 20 seconds or 10 breathing efforts. A one-way valve directed toward expiration can ensure that inspiratory efforts begin from a lung volume low enough to achieve maximal mechanical advantage. The $P_{AW}$ during the MIP maneuver should be measured continuously, either with a needle gauge or (preferably) by a pressure transducer linked to recording apparatus. Ideally, the MIP is sustained for at least 1 second; a transient isometric pressure may bear little relation to true ventilatory muscle strength and endurance. The MIP is perhaps the only involuntary measure of muscle strength that is even moderately reliable. However, it should be kept in mind that the validity of MIP in uncooperative patients depends on the strength of ventilatory drive and that the intensity of a voluntary effort in a fully cooperative patient is likely to exceed that elicited by simple airway occlusion. If sufficient ventilatory drive can be elicited (e.g., by the addition of dead space tubing to the airway), the drive-stimulated involuntary MIP may approximate the voluntary MIP rather closely.

Measures of Endurance

Mechanical Reserve

Two simple indices of ventilatory power reserve—the ratio of $[V \dot{}}]_E$ requirement to maximal voluntary ventilation (MVV) and the $V_t/V_C$ ratio—were proposed long ago and occasionally used to predict the outcome of machine withdrawal. On empirical grounds, it has been suggested that ratios greater than 50% portend weaning failure. Interestingly, laboratory data confirm that only approximately 50% to 60% of the MVV can be sustained longer than 15 minutes without ventilatory fatigue. During mechanical ventilation, variability of the breathing pattern and involuntary estimates of inspiratory capacity are helpful in gauging the judging reserve and predicting endurance. In the presence of supportive clinical signs and a stable or falling minute ventilation, a
rapid shallow breathing index ($f/V_T$) exceeding 110 suggests an unsustainable breathing workload. This useful indicator has its limitations, however. For example, because relatively rapid shallow breathing patterns may be normal and appropriate for patients with restrictive conditions of lung or chest wall, they may generate $f/V_T$ ratios that are considerably exceed 100, without experiencing respiratory distress or failure.

**Electromyography**

In the physiology laboratory, an increasing ratio of the integrated diaphragmatic EMG signal to generated pressure suggests a declining ability of the muscle pump to respond to neural stimulation (i.e., fatigue). Another EMG index of interest characterizes the spectrum of frequencies represented within the diaphragmatic EMG signal. The high frequency to low frequency ratio ($H/L$) is a good indicator of ventilatory stress and may be a sensitive and specific indicator of developing fatigue. A catheter capable of monitoring diaphragmatic EMG has recently been introduced to clinical practice in association with the neurally adjusted ventilatory assist (NAVA) mode, and initial work suggests that it has promise for tracking dyspnea as well as diaphragmatic performance.

**Pressure-Time Index**

Measured accurately, the MIP can be used in conjunction with $&OV0440;_{\text{tot}}$ to judge endurance and the likelihood of weaning success. In the laboratory setting, a diaphragmatic $&OV0440;_{\text{tot}}$ greater than 40% (with $t/t_{\text{tot}} = 0.40$) or a PTI ($P_{\text{T}} = &OV0440;_{\text{max}} \times t/t_{\text{tot}}$) greater than 0.15 predicts the inability to indefinitely sustain a target workload. No confirmatory data are available yet for the specific clinical setting of the weaning trial.

**Sequential Measurements of Drive**

A practical indication of declining power reserve may also be provided by a comparison of drive indices (such as $P_{0.1}$, esophageal pressure swing, or diaphragmatic EMG) measured sequentially during the stress period. Patients who fail to increase ventilatory drive in response to increasing $\text{PaCO}_2$ are prone to alveolar hypoventilation and weaning failure. In the future, monitoring the response of such indices as $P_{0.1}$ to an imposed stress or to $\text{CO}_2$ loading may provide valuable clinical indications of breathing reserve.

**SUGGESTED READINGS**


Chapter 6
Airway Intubation

• Key Points

1. Noninvasive ventilation is not appropriate for patients who cannot protect the airway, for those who are obtunded or uncooperative, for those in whom unexpected loss of pressure or of enriched oxygen might be immediately hazardous, for those who require high levels of applied pressure, or for those who are hemodynamically unstable. In such cases, endotracheal intubation is the indicated intervention.

2. Orotracheal tube placement is the method of choice during emergencies and most critical care applications. Another option in elective situations is the nasotracheal route, which requires tubes of generally smaller diameter than tubes used for orotracheal intubation. Although nasotracheal intubation may prove more comfortable and stable in the conscious or active patient, it is associated with sinusitis, presents higher airway resistance, impedes secretion extraction, and is not recommended for long-term use.

3. Important complications of intubation include a variety of insertion traumas, gastric aspiration, hypoxemia, laryngospasm, esophageal intubation, right main bronchus intubation, cardiac arrhythmias, and hemodynamic impairment. Assurance of adequate circulating volume to withstand the conversion from spontaneous to positive pressure breathing is advisable prior to the attempt.

4. Predictors of difficult intubation include nonvisibility of key oropharyngeal landmarks, poor atlanto-occipital joint mobility, mentothyroid distance less than 6 cm, mentosternal distance less than 12 cm, and restricted temporomandibular joint excursion. In such cases, the need for high-level expertise and specialized tools for airway management should be considered before the attempt. Failed attempts at intubation increase complication risk.

5. Instruments and techniques facilitating the intubation process include fibrobronchoscopy, lighted stylet guidance, video laryngoscopes, directed-tip endotracheal tubes, bougie catheters, and (rarely) retrograde wire insertion. Traditional methods to confirm tracheal positioning of the endotracheal tube include symmetry of breath sounds, ease of manual insufflation, complete recovery of insufflated tidal volume, loss of voice, expansion of the upper chest, squeeze bulb or syringe recovery of injected gas volumes, and coughing with expulsion of airway secretions. Currently, color-changing CO$_2$-sensing indicators play an important role for this purpose.

6. Inadvertent extubation in the critically ill is often a life-threatening event that occurs more commonly in orally intubated, lightly sedated patients (who must be carefully restrained). The ability of positive end-expiratory pressure to blow gas freely around a deflated cuff gives some assurance of patency of the larynx above the cuff immediately before a planned extubation.

7. Although its long-term complications can be serious and lifestyle inhibiting, short-term tracheostomy for the management of acute illness improves comfort, communication, secretion management, and mobility as well as allows intermittent disconnection of the ventilator. Certain variants of conventional tracheostomy (e.g., percutaneous dilatational tracheostomy, and minitracheostomy) do not require an operating room and often prove more convenient or safer to perform in well-selected acutely ill patients.
INDICATIONS

Primary indications for endotracheal (ET) intubation include (1) the need for assisted ventilation or the delivery of high levels of inspired oxygen, (2) airway protection against aspiration, (3) clearance of secretions retained in central airways, and (4) relief of upper airway obstruction (Table 6-1).

Table 6-1. Indications for Oral Intubation, Nasal Intubation, and Tracheostomy

<table>
<thead>
<tr>
<th>Oral</th>
<th>Nasal</th>
<th>Tracheostomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergent intubation (cardiopulmonary resuscitation, unconsciousness, or apnea)</td>
<td>Cervical spine ankylosis, arthritis, or trauma</td>
<td>Inability to insert translaryngeal tube</td>
</tr>
<tr>
<td>Nasal or midfacial trauma</td>
<td>Oral or mandibular trauma, surgery, or deformity</td>
<td>Obstruction above cricoid cartilage</td>
</tr>
<tr>
<td>Basilar skull fracture</td>
<td>Temporomandibular joint disease</td>
<td>Complications of translaryngeal intubation</td>
</tr>
<tr>
<td>Epiglottitis</td>
<td>Awake intubation</td>
<td>Glottic incompetence</td>
</tr>
<tr>
<td>Nasal obstruction</td>
<td>Gagging and vomiting</td>
<td>Inability to clear tracheobronchial secretions</td>
</tr>
<tr>
<td>Paranasal disease</td>
<td>Unusually short/thick neck</td>
<td>Sleep apnea unresponsive to CPAP</td>
</tr>
<tr>
<td>Bleeding diathesis</td>
<td></td>
<td>Facial or laryngeal trauma or structural contraindications to translaryngeal intubation</td>
</tr>
<tr>
<td>Need for bronchoscopy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Need for Assisted Ventilation and Positive End-Expiratory Pressure

Intubation of the trachea with a cuffed tube remains the only viable option for simultaneously securing the airway, allowing repeated access to the trachea, and providing effective ventilatory support with elevated positive pressure. Recent advances in noninvasive ventilation, however, mandate that clear indications for airway intubation be present (see Chapter 7). Tracheal intubation is required when high levels of airway pressure must be applied to ensure satisfactory oxygen exchange or ventilation. Moreover, noninvasive ventilation may not be appropriate or safe for patients who are obtunded or uncooperative, for those in whom even momentary loss of ventilatory pressure or inspired oxygen might be hazardous, for those requiring high levels of applied pressure, and for those who are hemodynamically unstable. When ventilatory support must be continuous and extended more than a few days, intubation clearly is a better approach.

Airway Protection

Because protection of the airway cannot be ensured without establishing an effective seal, intubation is required for lethargic or comatose patients at high risk for aspiration. Although an inflated cuff prevents massive airway flooding, small quantities of pharyngeal contents are aspirated routinely. Seepage of the infected secretions that pool just above the cuff may help account for the high incidence of pulmonary infections that occur in mechanically ventilated patients. Special tubes that allow continued evacuation of this secretion pool have been reported to reduce the incidence of ventilator-associated pneumonia (see Chapters 8 and 26).

Secretion Clearance
Retained airway secretions predispose to infection, encourage atelectasis, promote hypoxemia, and dramatically increase the breathing workload for patients with neuromuscular weakness and/or underlying airflow obstruction. Translaryngeal intubation and tracheostomy facilitate extraction of these secretions.

**Upper Airway Obstruction**

Intubation addresses the immediate threat of anatomic or functional obstruction of the upper airway and is often the first step taken before attempting definitive treatment (see Chapter 25).

### TYPES OF AIRWAYS AND ROUTES OF INTUBATION

#### Supraglottic Airways

Pharyngeal airways are firm supports placed through the nose or mouth that are intended to bypass the relaxed tongue, thereby splinting open the retropharynx and aiding access to the hypopharynx.

#### Oropharyngeal Airways

Oral airways are anatomically contoured plastic devices that displace the tongue from the posterior wall of the pharynx to prevent occlusion. Their primary purpose is to wedge open the hypopharynx and to facilitate secretion extraction during spontaneous breathing or bag-mask ventilation in patients who are not fully conscious. Well-placed oropharyngeal airways allow unimpeded spontaneous or assisted ventilation and facilitate removal of airway or pharyngeal secretions. They are not intended to substitute for ET intubation in patients with firm indications for airway protection or who require secure access to the lower airway.

An oral airway can also serve as a “bite block” for an orally intubated patient inclined to jaw clenching. Because they stimulate the retropharynx and promote gagging, oral airways must not be used in alert patients or in those with active gag reflexes. (Over time, however, some accommodation to this foreign object may develop.) Disturbingly, obtunded patients with depressed gag reflexes are just those who are most inclined to aspirate. These oropharyngeal airways must, therefore, be removed as soon as consciousness returns or evidence for an activated gag reflex appears.

#### Nasopharyngeal Airways

These firm (but compressible), curved, flanged, and hollow tubes (nasal “trumpets”) are available in a variety of diameters and lengths, but none are designed to extend into the glottis. They are inserted through a lubricated, topically anesthetized, and widely patent nasal passage to facilitate extraction of secretions from the hypopharynx or to guide the passage of tracheal suction catheters without repeated trauma to the nasal mucosa. For some patients, they are especially useful in the period immediately after extubation, when swallowing of oropharyngeal secretions and effective coughing may be impaired. Because they induce considerably less pharyngeal stimulation than do oral airways, they can be used for conscious patients and may serve temporarily as an effective conduit for topical anesthetic delivery to the retropharynx and larynx prior to intubation. Nasopharyngeal airways impede sinus drainage and are best transferred to the alternate nasal passage on a daily basis. Continuous use beyond 48 to 72 hours is generally inadvisable because of the escalating risk of infective and erosive complications. Although occasionally helpful in keeping the retropharynx open, they do not reliably maintain airway patency and are not an acceptable alternative to ET intubation for high-risk patients.

#### Laryngeal Mask Airway, King Airway, and Combitube

The laryngeal mask airway (LMA) is a device that is intended to be inserted into the pharynx without direct
visualization of the glottis while allowing effective ventilation and isolation of the lungs from the esophagus (Fig. 6-1). Levels of positive pressure ≤20 cm H₂O can be effectively applied. The insertion technique is rather easily mastered and can be implemented without deep anesthesia. Initially, the LMA was intended exclusively for emergent out-of-hospital resuscitation, but currently, it is used in surgical procedures and noninvasive and interventional radiologic procedures of short or intermediate duration (<2 hours). Increasingly, it is an immediate stopgap measure when ET intubation cannot be immediately established. LMA does not offer reliable protection from aspiration, but new designs (like the LMA ProSeal device [Teleflex Medical Europe Ltd, Dublin, Ireland]) can facilitate gastric suctioning and decrease the risk of aspiration. In the intensive care unit (ICU) environment, the LMA may have applications as well; for example, it allows for insertion of a bronchoscope-guided ET tube via an on-board channel while supporting ventilation. An LMA can therefore serve as a useful backup option for intubating—or reintubating—the difficult airway (LMA is included in the American Society of Anesthesia’s Difficult Airway Management Algorithm). For emergent placement of a reliable airway, the dual-lumen airway may represent the easiest and most reliable option (Fig. 6-2). The dual-lumen (King [Ambu, Copenhagen, Denmark], Combitube [Moore Medical, Farmington, CT]) airways are cuffed perforated tubes that perform as a combined tracheal conduit and esophageal obturator that allows gastric access. They are usually are inserted blindly and yet afford with relative assurance both ventilation of the lungs and some protection from aspiration.

Endotracheal Intubation

**Orotracheal Tubes**

As a rule, orotracheal (OT) tubes are easier to insert than are nasotracheal (NT) tubes, making oral placement the method of choice during emergencies. The larger tube passed by the oral route improves both airway resistance and secretion management and allows passage of a standard caliber fiberoptic bronchoscope (FOB), should the need arise. Variations of OT tubes are available that allow selective main bronchial intubation, allow aspiration of supraglottic secretions (above the cuff), allow direct fiberoptically imaged visualization of the trachea and main carina, provide an intramural lumen for dead space washout by fresh gas injected near the tube tip, and offer a variety of other unusual and occasionally useful functions. However, oral tubes are not without disadvantages, as they are less stable and less comfortable than are nasal tubes, and they impair swallowing to a greater extent. Most self-extubations occur in patients who are orally intubated. They often require an additional oral appliance for stabilization and to prevent tube occlusion by biting. During insertion, OT tube placement incurs a higher incidence of retching, vomiting, aspiration, and mainstem bronchus intubation than does the nasal approach, and oral tubes seriously compromise oropharyngeal hygiene. Finally, conventional OT intubation should only be attempted with care and precautions in patients with limited neck mobility (e.g., ankylosing spondylitis, rheumatoid arthritis, cervical spinal trauma, or prior surgery). Devices are now available to facilitate OT intubation and airway management in such difficult cases. These include fiberoptic intubating bronchoscopes, illuminated stylets, video laryngoscopes, and gum elastic bougies (see below).

Nasotracheal Tubes

NT tubes present comparatively high resistance to airflow because their lumens are of smaller caliber, kink easily, and tend to be easily compromised by secretions. The nares do not admit tubes as large as those that the oropharynx will accept. NT tubes are often difficult and sometimes painful to insert. Traumatic complications of NT tube insertion include damage to turbinates, polyps, and well-vascularized mucosa. Insertions should never be forced and should not be attempted in patients who do not easily admit a lubricated nasal trumpet on the same side. Severe hemorrhage can result from ill-advised nasal intubation attempts in patients predisposed to bleed. Coagulopathy, narrow or deformed nasal passages, and large nasal polyps are contraindications. In a significant percentage of patients, purulent nasal discharge or sinusitis develops, usually after 72 hours. Once in place, however, nasal tubes allow somewhat better communication, swallowing, mouth hygiene, and anchoring than do their oral counterparts. Nasal tubes offer clear advantages for patients with cervical spine disease and for those with a variety of oral, mandibular, and temporomandibular problems.

Physiologic Responses to Intubation

During the intubation of a lightly anesthetized normal adult, increases of heart rate and blood pressure are mediated by neural reflexes, catecholamines, and stress hormones. Moreover, bradycardia, cardiac arrhythmias, and arterial hypotension can be provoked. These cardiovascular effects are blunted by sedatives, analgesics, and systemic or topical anesthetics. Midazolam is frequently used before the procedure begins. Certain intravenous anesthetics frequently elicit hypotension, especially in patients with hypovolemia. In current ICU practice, a frequent offender is propofol, which should be given at less than customary rates in the elderly, debilitated, and critically ill. Ketamine, a drug with fewer hemodynamic side effects commonly used for intubations in the operating theater, preserves laryngeal and pharyngeal reflexes but is not recommended in patients with raised intracranial pressure, except if the patient is hypovolemic and hypotensive. Etomidate is frequently used and is generally safe and effective; however, this drug has been reported to interfere with adrenocortical output for more than a day after the dose is given (but any clinical impact is questionable). Laryngoscopy can impressively raise intracranial pressure, and special precautions to minimize this effect are indicated for patients with head trauma or other at-risk condition. Clinically significant laryngospasm and bronchospasm occur infrequently in a well-prepared subject.

An ET tube cannot exceed the caliber of the site of greatest narrowing within the native airway. Consequently, intubation reduces the dead space of the upper airway by 20 to 60 mL but simultaneously increases the resistance to airflow. Moreover, once inserted, the resistance offered by a bent, kinked, secretion-lined, or clot-obstructed ET tube in situ can be considerably greater than its manufacturing specification. Although certain reports suggest that intubation itself reduces the resting lung volume and alters the breathing pattern, the available evidence is conflicting, and there is no firm consensus on these points.

Complications of Airway Intubation

Anatomic Impairment

ET tubes bypass the mechanical defenses of the upper airway, contaminate the lower airway, and severely hamper effective coughing. Despite advances in materials and cuff design, all tubes have the potential to inflict laryngeal and tracheal injury during insertion, and none completely protect the lungs against aspiration of liquids. Furthermore, the supraglottic pool of oral secretions that seep past the cuff as well as the biofilm that routinely lines the lumen of the tube serve to repeatedly inoculate the lower airway with potential pathogens.

Insertion Trauma
Inexpert placement of an ET tube may injure delicate labial, laryngeal, nasal, and pharyngeal tissues or cause dental or spinal trauma. Epistaxis occurs in a sizable percentage of patients who are intubated nasotracheally. Mouth trauma, tooth dislodgement, and mandibular dislocation can result from forceful use of the laryngoscope and placement of an OT tube. Most laryngeal and tracheal injuries that result from intubation with normally inflated tubes having soft, high-volume cuffs are mild and easily healed. The formation of granulation tissue and ulcers in the glottis and upper trachea by pressure-induced mucosal ischemia, although uncommon, can cause major long-term trouble. Such complications may be observed when tight-fitting (oversized) ET tubes and unrelieved excessive cuff pressure are used for long durations. Vocal cord injuries/paralysis and arytenoid cartilage dislocation typically present as postextubation hoarseness and upper airway obstruction. Use of a nasogastric tube in conjunction with oral intubation has been associated with a higher incidence of aspiration, mucosal erythema, and granuloma formation. Very rarely, tracheoesophageal fistula may form after prolonged intubation with a poorly managed ET tube.

Hypoxemia
Patients who require supplemental O\textsubscript{2} often are exposed to room air during intubation, with consequent desaturation of arterial blood. Although this risk is reduced by “preoxygenation,” O\textsubscript{2} stored in this way is depleted quickly by deep breathing, especially in patients with seriously impaired gas exchanging function. Therefore, intubation attempts should not be prolonged beyond 30 seconds before “reoxygenating,” especially for patients who continue to breathe actively. Pulse oximetry provides a useful but delayed signal that helps warn of developing hypoxemia during the attempt. Nasal prongs set to deliver >8 L of oxygen per minute can provide supplemental O\textsubscript{2} during oral intubation, as can the more efficient high-flow nasal cannula (40 to 60 L/min) or the use of a laryngoscope adapted for this purpose.

Apneic, Rapid Sequence, or Ventilation-Assisted Intubation
Depletion of the pulmonary oxygen reservoir can be slowed by maintaining a high FiO\textsubscript{2} within the lung during the attempt at tube placement. This supplementation is effected by first giving a rapidly acting hypnotic agent (e.g., propofol 2 mg/kg, ketamine, or etomidate 0.3 mg/kg intravenously) together with midazolam (amnesic agent, 1 to 5 mg) and an opioid analgesic intravenously. These are followed quickly by an ultra-short-acting depolarizing muscle relaxant (customarily, succinylcholine 1 to 2 mg/kg IV) that has onset time less than 60 seconds. Nondepolarizing muscle relaxants, such as rocuronium (0.6 mg/kg) or vecuronium (0.08 mg/kg), are alternatives with an onset time less than 3 minutes, are longer acting, and are less often associated with potassium release or other adverse complications that sometimes occur in patients with extensive burns, immobility, and motor neuron disease. This intubation technique also facilitates cannulation of the larynx, permits control of ventilation, and lessens the hazards of laryngospasm and insertion trauma. Although rapid sequence, apneic intubation is often the preferred technique in difficult cases, sedatives and muscle relaxants are not without risk. Relaxed musculature may totally obstruct the upper airway if the intubation attempt is unsuccessful, and barbiturates and propofol may depress cardiac contractility and promote hypotension. The clinician must be certain that manual ventilation by face mask is effective before committing to muscle relaxation, and expert assistance must be immediately at hand. High-flow nasal oxygen may help delay onset of hypoxemia during the intubation attempt. Implements for immediate surgical intervention to establish an airway must be at the bedside before the attempt. Succinylcholine rarely induces hyperkalemia or (even more rarely) precipitates “malignant hyperthermia” but is a higher risk in patients with compatible family history.

In general, the blind NT approach should not be attempted during emergent intubation because of the uncertain time required to secure the airway. Moreover, blind NT intubation is exceedingly difficult if the patient is apneic.
Fiberoptic bronchoscopy, direct laryngoscopy, and video laryngoscope may facilitate semi-emergent placement of either type of ET tube.

**Gastric Aspiration**
Stimulation of the oropharynx may easily cause vomiting, especially when the stomach is distended by food or air or the patient is not well sedated. In patients with high risk for gastric aspiration, application of gentle cricothyroid pressure (Sellick maneuver) from the start of bag-mask ventilation helps seal the esophagus against air entry and helps bring the cords into view but does not obviate the risk of aspiration. Prior evacuation of the stomach can reduce the aspiration risk; however, gastric decompression should not delay emergent intubation. Patients with high risk for gastric aspiration who will undergo planned surgery can electively receive histamine-2 blocker (ranitidine) and/or prokinetic agent as metoclopramide to decrease this risk.

**Reflex Glottic Closure and Laryngospasm**
Reflex closure of the glottis and true laryngospasm can prevent passage of the ET tube and may severely limit spontaneous ventilation. Prior use of a topical anesthetic (e.g., lidocaine, 4%) or intravenously (1 to 2 mg/kg for 3 to 5 minutes before intubation) minimizes the risk. In rare individuals, however, lidocaine is irritating and may itself provoke spasm. Rather than attempt forceful intubation (losing valuable time and risking laryngeal trauma), the patient should be ventilated by bag-mask insufflation of oxygen. Spasm usually subsides promptly. However, if adequate ventilation cannot be achieved and the situation becomes urgent, intravenous succinylcholine (1 mg/kg IV) will relax the contracted muscles during ET tube placement. Repeated failure suggests that a bougie, stylet, fiberoptic guide, or other intubation aid is necessary.

**Bronchospasm**
Tube placement often stimulates irritant receptors, triggering cough and bronchospasm. Such receptors stop firing shortly after tube placement in most cases, unless the tip of the tube continues to touch the carina. In nonemergent cases at higher risk for bronchospasm, prior administration of aerosolized albuterol, ipratropium, or their combination may prove helpful. Infused or aerosolized bronchodilators may relieve bronchospasm but leave the mechanically stimulated coughing reflex unaffected. Although coughing postintubation is often difficult to arrest, an ET bolus of lidocaine (5 mL of a 2% solution) may be temporarily effective.

**Right Main Bronchus Intubation**
In emergent situations, there is a natural tendency to advance the ET tube beyond the carina. The right main bronchus is less sharply angulated from the trachea than is the left main bronchus and will be entered in a high percentage of low placements. Rarely, this tendency may facilitate intentional isolation of the right and left lungs during management of such problems as massive hemoptysis originating distal to the main carina. The underventilated left lung and right upper lobe may collapse rapidly, especially when previously ventilated with oxygen. Although comparative auscultation is helpful, breath sounds often are surprisingly well transmitted to an underventilated lung. Bedside ultrasound may provide quick and effective imaging guidance.

ET tubes should be advanced a maximum of 2.5 to 5.0 cm beyond the point at which the tube cuff is seen to pass the level of the cords. Use of a lighted stylet facilitates tip localization to the appropriate level. The distance from the frontal incisors to the carina, which is height dependent, is approximately 28 cm in an average man and 24 cm in an average woman. As a general rule, 23 to 24 cm and 21 to 22 cm at the lips, respectively, will approximate the proper tube tip position in adult men and women of average size. A postprocedure chest X-ray is necessary to check the position. A generous distance (at least 3 cm) between tube tip and main carina must be allowed for tube movement because of spontaneous neck flexions.
POINTS OF TECHNIQUE

Intubation of a rapidly deteriorating, critically ill patient can be a dramatic clinical event. In these challenging circumstances, success depends on optimal preparation and experience of the operator proportional to the anticipated difficulty of successful insertion. Assuming that any deficit of intravascular volume has already been addressed, certain important questions should be addressed before the attempt: (1) Is intubation of the airway likely to be anatomically challenging? If so, who should attempt the intubation? (2) Which is the best approach—oral, nasal, or tracheostomy? (3) Should the attempt be made awake, under sedation, or using rapid sequence (apneic) technique? (4) Is the patient at unusually high risk for aspiration? (5) What is the contingency approach (“backup plan”)? (6) Are all necessary materials and personnel at hand to support both the primary and backup plans?

When undertaking the intubation of the airway of a critically ill patient, the physician is obligated to make sure that all appropriate equipment, drugs, personnel, and preparations have been brought to bear. Bag-mask ventilation is not invariably effective, and a secondary “backup plan” to secure the airway should be in place for immediate implementation should the first attempts to cannulate the airway fail. In some cases, this may mean ensuring the immediate availability of an anesthesiologist, readiness to attempt an alternative mode of intubation (e.g., apneic or rapid sequence), temporary use of an LMA, or performance of needle cricothyroidotomy or emergent surgical tracheostomy. Similar precautions should be taken when a patient with a known or potentially difficult airway is extubated. The most difficult intubation cases may best be managed in the operating theater, when time and circumstances allow.

The Difficult Airway

In a significant minority of critically ill patients, even a practitioner who is well trained in conventional intubation techniques will experience difficulty with mask ventilation or tracheal intubation. Such problems assume particular importance for the critically ill patient who is hypoxemic, acidotic, or hemodynamically unstable. A plan of action and preparedness for difficult intubation are essential for safe practice. Although prediction of who will present unusual difficulty is not precise, certain “red flag” features are worth noting. Abnormal facial anatomy, inability to fully open the mouth, pharyngeal and laryngeal abnormalities, and cervical immobility or anomalies account for the vast majority of problems. Very obese patients with short necks and/or increased neck circumference often present problems. Other physical features correlate (although quite imperfectly) with the difficulty of intubation (Fig. 6-3). These include the nonvisibility of key oropharyngeal landmarks: faucial pillars, soft palate, and uvula; poor atlanto-occipital joint mobility (<30-degree excursion of the maxillary teeth, neutral to fully extended); short mentohyoid distance (less than three finger breadths); mentothyroid distance less than 6 cm; interincisor distance less than 4.0 cm; sternomental distance less than 12 cm; and restricted temporomandibular joint excursion (maximal oral aperture height less than three finger breadths in the sagittal midline) (Table 6-2). Special caution should be exercised in the presence of a small mouth, large tongue, inability to widely open the mouth, immobile neck, anterior larynx, prior spine surgery, cervical arthritis/arthrosis, and neck masses. Perhaps surprisingly, edentulous patients often present intubation difficulty. Helpful techniques are now available for consideration in such circumstances (Table 6-3).

Aids for Difficult Intubation

The BURP Maneuver

Mandibular advancement alone or combined with backward, upward, and rightward pressure on the cricoid cartilage (BURP maneuver) may improve the view during direct laryngoscopy (Table 6-4).

The BURP is best performed initially by the person attempting to view the cords, with an assistant helping the
intubator during the attempt itself.

**FIGURE 6-3. Evaluating the airway for ease of intubation.**

A: A patient who cannot be intubated easily will have poorly defined oral landmarks (uvula, faucial pillars, and epiglottis) during tongue protrusion. B: The mouth aperture should be sufficient to allow entry of three finger breadths on widest opening. C: Mobility of the atlanto-occipital joint is ensured by the ability to incline the occlusal surfaces of the maxillary molars by 30 degrees or more from the neutral position. D: Finally, the chin should allow separation from the hyoid bone by three finger breadths or more. Failure to meet these criteria indicates a potentially difficult oral (and perhaps nasal) intubation.

**Airway Exchange (Oxygenating) Catheters**

As their name implies, these relatively small-diameter tubes act as hollow guides over which to guide a fresh tube after another has been removed in a high-risk patient, or less frequently, as an introducer during the initial intubation. The fresh gas source helps to “buy time” for patients at high risk to rapidly desaturate or suffer adverse consequences of temporary hypoxemia.

**Table 6-2. Predictors of Difficult Intubation**

| Invisibility of faucial pillars, soft palate, uvula |
| Mentohyoid distance less than three finger breadths |
| Restricted temporomandibular joint excursion |
Bronchoscope-Guided Airway Management

A FOB may be used to place an oral or nasal tube, position a double-lumen or single-lumen tube, or assess the feasibility and advisability of extubation. Although this procedure may be particularly helpful for patients with difficult airways or poor neck mobility, the field of view is obscured easily by secretions, vomitus, or blood. Bronchoscopic assistance may be useful when an exchange of tubes necessitated by cuff rupture or luminal narrowing and can be conducted in a semielective time frame. Video laryngoscopy has obviated some of the intubation roles previously assigned to FOB.

Table 6-3. Techniques to Aid Difficult Intubation

- Forceps-guided insertion
- Stylet- or bougie-guided insertion
- Specialized laryngoscopes (e.g., video)
- Retrograde intubation

Table 6-4. Aids and Precautions for Difficult Intubation

- Optimal positioning
- Availability of:
  - Video laryngoscope
  - Gum elastic bougies
  - Tracheal tubes of various sizes
  - Tube introducers
  - Varied types and sizes of laryngoscope blade
  - Lighted stylet
  - LMA and cricothyroidotomy kit
- BURP maneuver

Forceps-Guided Intubation

When difficulty is encountered in entering the larynx using a nasal approach (or when exchanging an oral for a
nasal tube), McGill forceps can be used to grasp the tip of the nasal tube as it enters the retropharynx, directing it through the vocal cords under direct laryngoscopic observation.

**Bougie**
The bougie (or gum elastic bougie), a small-diameter semiflexible tube (Fig. 6-4), serves a similar function as a stylet, but the process is often a sequential one and may not require laryngoscopic visualization of the glottis opening. The process resembles the Seldinger technique for vascular cannulation in that the bougie acts as a slender rail guide over which the tube is later gently advanced. The bendable and purpose-shaped bougie is inserted in the midline and directed anteriorly.

![Flexible bougie inserted through an OT tube.](image)

**FIGURE 6-4. Flexible bougie inserted through an OT tube.** The angulated tip of this variant may prove useful when entering the glottis of a difficult airway. Once in the trachea, the bougie serves as a guide (“stylet”) for the ET tube.

**Stylet-Guided Intubation**
Various forms of stylet can be used to direct the pliable ET tube into the glottic aperture more easily. These deformable metal or plastic rods span a range from the standard aluminum rods to flexible guides with thumb triggers, which give the operator the ability to direct the tube tip at any time during the insertion attempt. Unlike the bougie or oxygenating catheter, the tip of the stylet is kept within—not beyond the ET tube—and is often formed into a tip-angulated “hockey stick” shape for optimal insertion of the laryngoscopically guided tube into a poorly seen glottic aperture. The stylet is withdrawn once the tube passes the cords. Neither the stylet nor the ET tube should ever be forced through the glottic aperture, as damage to the delicate cartilaginous ring may occur.

**Illuminating Stylets**
A battery-operated illuminating stylet (“light wand”) has a very bright tip that transilluminates the skin above the thyroid cartilage as it enters the larynx. This “jack-o’-lantern” effect fails to be seen distinctly when the tube enters the esophagus. The light wand accurately guides the ET tube passage in a very high percentage of blind
ET intubations (reportedly >95%). This device does not require the sniffing position or laryngoscopy but requires partially dark room. The light wand has limitations in patients with a very thick neck (e.g., short obese patient) because of difficulty in achieving transillumination.

**Specialized Laryngoscopes**

For many years, the primary options for cord visualization were straight and curved blade laryngoscopes, and most clinicians have developed facility with (or preference for) one or the other of them. In response to clinical need, specialized blades that incorporate a variety of desirable features are now available. These range from innovatively shaped blades (V-form, double-angled, tube-shaped, and hinged-tip configurations) to blades that incorporate flexible fiberoptic bundles to aid visualization videoscopically or ports to facilitate oxygen delivery and suctioning.

**Retrograde Intubation**

When elective or semielective ET intubation is indicated but the cords defy passage by other methods, a flexible guidewire inserted retrograde through the needle-punctured cricothyroid membrane can be advanced through the mouth to establish the pathway for an introducer and/or tube. With the current availability of simpler aids to intubation, this method is now seldom used and is best performed by an experienced operator.

**Distinguishing Tracheal from Esophageal Intubation**

Although unquestionably useful, traditional methods for confirming the ET placement of the tube have limited reliability (Table 6-5). These techniques include stethoscopic audibility and symmetry of breath sounds, direct visualization of the cords during insertion, ease of insufflation and recovery of the tidal volume, tidal fogging and clearing of the ET tube, palpation of the ET tube in the larynx, loss of voice, coughing and expulsion of airway secretions, expansion of the upper chest, and failure of the abdomen to progressively distend during gas delivery.

### Table 6-5. Distinguishing Tracheal from Esophageal Intubation

<table>
<thead>
<tr>
<th>CONVENTIONAL</th>
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<tr>
<td>Symmetrical breath sounds</td>
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<tr>
<td>Visualization of vocal cords during insertion</td>
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<tr>
<td>Ease of insufflation and recovery of tidal volume</td>
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<tr>
<td>Expiratory fogging of ET tube</td>
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<tr>
<td>Palpation of larynx</td>
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<tr>
<td>Loss of voice</td>
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<tr>
<td>Coughing of airway secretions through tube</td>
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<tr>
<td>Upper chest expansion</td>
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<td>Absence of progressive abdominal distention</td>
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<tr>
<th>DEVICES AND AIDS</th>
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<tbody>
<tr>
<td>CO₂ excretion color detector</td>
</tr>
<tr>
<td>Capnometry</td>
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<tr>
<td>Tidal gas recovery</td>
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</tbody>
</table>
Pulse oximetry, which is useful in ensuring optimal arterial oxygenation during the procedure for patients with adequate cardiac output, may also help in the evaluation of correct placement. To improve reliability and speed, the phasic detection of CO\(_2\) during expiration by capnography and capnometry can be performed. These devices can be sidestream or mainstream; the latter is more sensitive and more commonly used because it does not require suctioning of gas from the ET connector. For emergent intubations, these devices are not generally available, and a simple color-changing indicator gives an adequate qualitative assessment for most patients. Carbon dioxide detection and measurement by these methods occasionally can be misleading. Little CO\(_2\) is evolved or expelled during shock or circulatory arrest, and conversely, some CO\(_2\) may be liberated initially after esophageal intubation from gas trapped in the gastric pouch. However, this concentration falls rapidly as serial tidal volumes are delivered. Reliability of the detector may be compromised when it is soiled by gastric secretions.

When compressed, a large-capacity squeeze bulb affixed to the ET tube will fail to fill easily if the tube is in the collapsible esophagus. If in good position, however, it recoils effortlessly to its resting volume. Free withdrawal of air via a fitted 50-mL syringe is an equivalent if inexact and not completely reliable method based on the same principle.

**Intubation Sequence**

**Sedation and Neuromuscular Blockade**

Rapidly acting benzodiazepines impart amnesia, usually without significantly affecting hemodynamics. Intravenous midazolam, a rapidly acting drug of this class, has a convenient onset (1 to 3 minutes) and duration (approx. 20 minutes). Fentanyl or similar narcotic agent often provides effective analgesia. Propofol, given as a bolus dose, has a near-immediate onset of action and duration of 7 to 10 minutes. When required, muscle relaxation can be accomplished with depolarizing (succinylcholine) or nondepolarizing (vecuronium, rocuronium) agents. Etomidate is the ideal induction agent to hold hemodynamic variables unaffected, but it is interesting to note that even a single dose can interfere with determinations of serum cortisol. Ketamine is also a good choice in cases with hypovolemia or hypotension.

**Oral Intubation**

Apart from being well prepared for emergent developments, perhaps the most important thing for the intubating physician to do is to relax and avoid panic. After clearing the airway of secretions and debris, the base of the tongue is displaced from the retropharynx by lifting at the angles of the jaw. Unless contraindicated, the patient should be positioned with the head (not shoulders) resting on a thin pillow or a doubly folded towel. The optimal “sniffing” position is with the chin lifted, neck flexed, and the head extended (Fig. 6-5). Once positioned, the patient generally can be ventilated by mask without difficulty until the tube is inserted. For obtunded or comatose patients, an oropharyngeal airway can be inserted to maintain the passage, but such devices may stimulate vomiting in the conscious or agitated subject, and in such cases, nasopharyngeal airway may be better. Bag-mask insufflations should be delivered gently (never forcefully) at a measured rate. During a cardiac arrest in a patient with severe airflow obstruction, special care should be taken to avoid overventilation and iatrogenic “auto positive end-expiratory pressure (auto-PEEP).” If tube placement is not emergent, an alert patient should be lightly sedated and a topical anesthetic used. When oral secretions are copious, the antisialagogue glycopyrrolate (0.2 mg IV), given prior to elective intubation, can help preserve a well-visualized field. An alert,
cooperative patient can be instructed to pant to concentrate deposition of aerosolized 4% lidocaine on the larynx and upper airway. As a rule, agitated or seriously hypoxemic patients should be sedated and paralyzed quickly (rapid sequence, apneic intubation technique). However, this method must be used with special caution in patients who are massively obese and for those with upper airway pathology. In such cases, experienced personnel must be available, and the physician should have access to immediate, expert, and more experienced help. In very rare instances, cricothyroid puncture can be attempted if the airway totally obstructs after paralysis, bag-mask ventilation is totally unsuccessful, and attempts to intubate repeatedly fail. Even if phasic gas delivery is not undertaken, oxygen insufflated continuously through a large bore needle at 2 to 4 L/min can often maintain acceptable arterial oxygenation (and a degree of ventilation) without hyperinflation until a secure airway can be established.

**FIGURE 6-5. OT intubation.** To align the glottis, pharynx, and oral cavity, the neck is flexed and the head is extended. The laryngoscope lifts the tongue and lower jaw away from the posterior pharynx by a motion directed perpendicular to the oroglossal axis. **Inset:** View of the glottis provided by a video laryngoscope during intubation.

An 8.5-mm (internal diameter) tube for an average male and an 8.0-mm tube for an average female are good sizes to try first. The tube selected should generally be the largest that will easily pass through the cords. Curved laryngoscope blades are directed anterior to the epiglottis, with the tip in the vallecula (Fig. 6-5). Straight blades are inserted immediately posterior to the epiglottis and allow a better view of the cords. Both instruments should lift the entire jaw upward to expose the larynx. Neither instrument should use the teeth as a fulcrum for leverage. During intubation, firm cricothyroid pressure (BURP maneuver) helps to bring the cords into view and
to seal the esophagus.

When flexible stylets are used to direct the tip of the tube into a glottic opening that cannot be visualized clearly and continuously, care must be taken to ensure that the stylet does not project beyond the tip of the ET tube. After placement, the cuff should be inflated with the minimum volume that seals without leakage under positive pressure. A variety of useful devices is now available to stabilize an OT tube after placement. Lacking these, a standard ET tube can be anchored effectively by a continuous single band of padded tape wrapped circumferentially around the neck and secured to the tube (and bite block, if used) at both ends. The hands must be restrained if there is any possibility for self-extubation. This is especially important after OT intubation in a hypoxemic patient requiring high levels of inspired oxygen or airway pressure. Although a nasogastric or orogastric tube should be used for the orally intubated patient to decompress the stomach when there is gut hypomotility or active air swallowing, its continued use may increase the incidence of aspiration and laryngeal erosion.

Nasotracheal Intubation

Blind NT intubation is not a technique to be performed by the inexperienced caregiver. It should not be used in emergent situations and is particularly inappropriate for establishing the airway during apnea. Nasal intubation is especially hazardous in patients with coagulopathy. Because it is usually performed in awake patients, topical anesthesia of the nose, pharynx, and larynx, and sedation are mandatory. A topical vasoconstrictor (typically, phenylephrine) can facilitate tube passage and reduce the risk of mucosal hemorrhage. Before the intubation attempt, a lidocaine gel-lubricated nasal trumpet should be passed to calibrate the diameter of the passage and deliver topical anesthesia with minimal trauma risk. Selection of an appropriate tube (typically size 6.5 to 7.5), softened with hot water, generous nasal lubrication, and gentle insertion technique are necessary to prevent nasal, laryngeal, or tracheal injury. With the head in an upright orientation, the NT tube should be inserted initially to a level just above the vocal cords. This tube position can be confirmed using a FOB. Alternatively, that location can be detected by an expert who simply listens to the intensity of expired air flowing through the tube. The tube is then rapidly but gently advanced in synchrony with the next inspiratory effort. Passage through the larynx usually is signaled by a vigorous cough and subsequent inability to speak. Vigilance should be maintained against the development of sinusitis, which complicates approximately one third of placements longer than a few days.

Tube Exchange

Occasionally, a ruptured tube cuff, occlusion of the lumen with secretions or clot, or special care requirements unmet by the tube in place justify replacement. When ventilation or oxygenation needs are high, the changeout is best conducted under direct vision in an adequately sedated patient, using a conventional laryngoscope or a bronchoscope preloaded with the fresh tube to minimize the risk. Extracting the tube and proceeding as during a fresh intubation is hazardous, particularly in the presence of respiratory failure or laryngeal edema caused by disease or protracted intubation. Using a tube-changing catheter (e.g., bougie) is another option, and here again, laryngoscopy is indicated if airway anatomy is uncertain (Fig. 6-4). Deep sedation and paralysis are often required for safety. A tube changer is a long plastic tube (hollow or solid) that acts as a stent when a fresh ET tube is exchanged for a malfunctioning or less-desirable one. In an emergency, a tube changer can be improvised by trimming a standard nasogastric tube.

Extubation

Optimal preparation of the patient is essential before the tube is removed, with special attention given to fluid balance, electrolytes, and prevention of cardiac ischemia. Inadvertent or unplanned (self) extubation can
prove lethal in the acutely ill and must be avoided at all costs. Even planned extubation must not be performed casually. Extubation breaks the seal between the patient's upper and lower airways, potentially allowing purulent secretions pooled above the cuff to enter the lung. Reflex stimulation may also provoke laryngospasm, bronchospasm, or cardiac arrhythmias.

Oxygen should be administered, and the trachea and oropharynx cleared of secretions before the cuff is deflated. After a deep inspiration, the tube should be pulled quickly as the patient exhales forcefully from a high lung volume. One simple trick for helping the patient expel those above cuff secretions (rather than aspirate them as the tube is extracted) is to raise PEEP to 15 cm H₂O for 3 to 10 breaths before cuff deflation, maintaining the pressure target until after removal is completed. Doing so does three useful things: (1) breaks any existing “mucus seal” after cuff deflation, (2) expands the chest to reverse atelectasis and help with the force of the initial cough, and (3) generates and sustains a mouth-directed flow once the tube cuff is down, favoring expulsion.

Postextubation stridor may occur because of laryngospasm or edema. This usually subsides spontaneously within the first 6 to 24 hours if the head is held upright, but such patients must be observed carefully to assess the need for urgent reintubation. Although not routinely necessary, inhaled racemic epinephrine, bronchodilators, continuous positive airway pressure (CPAP), and corticosteroids may be helpful after extubation in selected cases—especially those involving small adults or children. Although the medical literature is somewhat inconsistent regarding efficacy, dosing, and timing, the general consensus is that corticosteroids (e.g., dexamethasone) given in anti-inflammatory doses for at least 12 hours prior to planned extubation are worthwhile in patients at high risk for stridor (e.g., failed cuff leak test). Sustained upright positioning and diuresis also make logical (if unconfirmed) sense in edematous patients.

The ability of the patient to inhale and exhale freely around the deflated cuff before extubation gives some assurance that the airway above the cuff is not severely narrowed. This simple test is useful when upper airway obstruction has been the primary indication for intubation. An audible leak around the partially deflated cuff during assisted ventilation is a sensitive predictor of successful extubation for a patient who meets other criteria for ventilator independence, but the absence of a cuff leak does not reliably predict extubation failure secondary to upper airway obstruction. Mucus and edema may form a temporarily effective but breakable seal. When they do, flow around the deflated cuff may sometimes be established by simple head positioning or ET tube advancement. Raising PEEP to 10 to 15 cm H₂O during volume or pressure assist-control may quickly dislodge the mucus. Failing that, upright positioning and pressure controlled ventilation and moderate PEEP (e.g., 10 cm H₂O) with the cuff deflated may cause the airway to reopen within 15 to 30 minutes as local edema and cuff-associated muscle tone gradually recede. (The low exhaled tidal volume alarm will prompt attention to a reopened passage.)

Noninvasive ventilation, applied with a humidified gas source to minimize secretion inspissation, may provide a useful bridge across the immediate postextubation period. High-flow nasal oxygen may serve a similar function in some patients but not those in need of substantial ventilatory support. BiPAP should be considered, not only to ease spontaneous breathing during waking hours but also to help assure adequate sleep in the first 24 to 28 hours after extubation. (Functional upper airway obstruction is common after tube removal because of local edema, increased laryngeal muscle tone, relief of alerting stress, and residual sedation.) In fragile patients with a weak cough, thickened secretions, and/or the need for frequent suctioning, consideration should be given preextubation to inspection of the lower airway for retained secretions. Heliox, a low-density helium-oxygen mixture (70:30, 80:20), reduces resistive pressure losses because of turbulence and may prove useful during the period of maximal edema for selected patients.

Women are predisposed to the long-term complications of intubation. Postextubation stridor may result from vocal cord dysfunction, arytenoid dislocation, laryngospasm, uncleared secretions or blood, or tracheomalacia. If
reintubation is needed, a smaller ET tube and a prophylactic epinephrine aerosol directed onto the cords are reasonable measures.

**Decannulating the Difficult Airway**

Edema, secretions, and local trauma often pose a challenge to reintubation, should that prove necessary. In the case of the airway whose cannulation proved tricky initially, the problem can rapidly advance from difficult to life threatening. In cases with such potential, it is essential to prepare for any contingency *before* the tube is removed. Readiness means having personnel with the required level of experience immediately available and to assure that the aforementioned intubation aids are kept nearby. For this emergent setting, stopgap stabilizing measures might include an LMA, noninvasive ventilation, and even a large bore needle with attachment tubing for cricothyroid membrane puncture and metered oxygen insufflation. Most importantly, both a strategy and sequence for effectively securing the airway postextubation should be thought through in detail—prior to decannulation.

**Postextubation Care**

The first 24 to 48 hours that follow extubation often present a serious challenge to the patient’s secretion-clearing mechanisms, as protective reflexes are blunted, laryngeal protection is transiently suboptimal, swallowing is impaired, and swelling of periglottic tissues increases airflow resistance. Furthermore, the patient may not remain consistently alert because of residual drug effects and sleep deprivation. During this time, maintaining secretion hygiene is an especially important goal. To minimize the aspiration risk, the patient should be cared for in the upright position and oral intake must be withheld until there is proof of effective swallowing. Noninvasive application of CPAP or BiPAP may help ensure upper airway patency and adequate nocturnal ventilation during this time. High-flow nasal oxygen is another useful option. Antisialagogues, such as glycopyrrolate, may be helpful if oral secretions are excessive and thin. Stridor in the immediate postextubation period may respond to aerosols of racemic epinephrine and relief of bronchospasm. Corticosteroids postextubation are often used, but as indicated earlier regarding stridor prevention, are of inconsistent value. When increased upper airway resistance is the primary problem, temporary use of BiPAP or heliox may help until upper airway swelling recedes. After 48 hours, many of these problems diminish. As noted in Chapter 10, the need for reintubation occurring after a brief period of spontaneous breathing portends a poor prognosis in the setting of critical illness.

| Table 6-6. Translaryngeal Intubation Versus Tracheostomy |
|---------------------------------|---------------------------------|
| **Translaryngeal Intubation**    | **Tracheostomy**                |
| Advantages                      |                                 |
| Ease of placement               | Comfort                         |
| Inexpensive                     | Ease of mouth care              |
| Fewer severe complications      | Secretion removal               |
| No specialized venue needed for | Stability                        |
| insertion                       | Less airway resistance          |
|                                 | Improved communication          |
|                                 | Ease of swallowing and enteral  |
|                                 | feeding                         |
|                                 | Reduced work of breathing       |
|                                 | Improved mobility               |
|                                 | Ease of reinsertion and ventilator |
Disadvantages

- Discomfort
- Swallowing
- Secretion clearance
- Greater work of breathing
- Impaired speech
- Upper airway and larynx damage

Disadvantages

- Expense
- Severity of complications
- Swallowing impairment
- Reduced cough efficiency
- postdecannulation

**TRACHEOSTOMY**

**Benefits and Indications**

Tracheostomy improves comfort (potentially allowing the patient to eat, talk, and ambulate), greatly facilitates secretion management, minimizes airway resistance and anatomic dead space, and reduces the risk of laryngeal injury ([Table 6-6](#)). However, tracheostomies have the highest associated risk of serious complications (bleeding, stenosis) and the highest incidence of swallowing difficulty and aspiration postextubation. Quality of life is impaired for those who need long-term tracheostomy. Unless carried out emergently for acute upper airway obstruction, conventional tracheostomy (but not necessarily **percutaneous** tracheostomy) should be performed over an oral or nasal tube in an operating suite. Except when long-term ventilator dependence or need for ongoing secretion management has been established, most experts defer tracheostomy for at least 10 days after intubation.

**Variants of Conventional Tracheostomy**

Certain variants of tracheostomy recently introduced to clinical practice may be carried out safely at the bedside.

**Needle Cricothyroidotomy**

In very rare circumstances, life-threatening upper airway obstruction renders invalid or infeasible all standard methods of airway control including pharyngeal airways, bag-mask ventilation, and translaryngeal intubation. Needle cricothyroidotomy can be performed quickly with a 14-gauge or larger needle to provide a temporary conduit for a high-pressure source of oxygen. After the cricothyroid membrane is located, prepared antiseptically, anesthetized, and immobilized, a syringe-mounted needle with external cannula punctures the membrane at a 45-degree angle, and air is aspirated to confirm its position. Once inserted, the outer flexible sheath is advanced as the metallic needle is withdrawn. Attachment of a Y-connector and high-pressure oxygen source at 40 to 60 L/min may then allow manually gated (phasic) insufflations, which usually maintain acceptable oxygenation until a definitive airway can be established.
An entirely different alternative to conventional tracheostomy has gained popularity as an elective (nonemergent) procedure for establishing long-term airway access, ventilatory support, and secretion clearance at the bedside for those patients who cannot be transported to the operating room (Fig. 6-6).

One of two operators uses a bronchoscope to both secure the air channel and to guide the needle puncture of the trachea under direct vision. Using a series of dilators and a modified Seldinger technique, the tube enters the trachea between the cricoid and first tracheal cartilage or between the first and second tracheal cartilages. After dissecting to the anterior tracheal wall, an introducer, sheath, guidewire, and catheter are used to progressively develop and dilate the stoma for acceptance of a standard tracheostomy tube. Bleeding, subcutaneous emphysema, and paratracheal insertion are reported complications. The incidence of infection is believed to be less than with the open surgical approach, but overall incidence rates of late complications are similar.
**Minitracheostomy**

When secretion retention is the primary concern, a minitracheostomy may be performed to allow suctioning through a small-diameter (4.0-mm) cuffless indwelling cannula that can also serve as an O₂ delivery conduit. Although inadequate for ventilation, transtracheal insufflation via the “Mini-Trach” can be helpful in an emergency. Candidates for the Mini-Trach should have an intact gag reflex because the airway is not protected. This device does not seriously impede talking, coughing, or eating.

**Tracheostomy Tube Displacement**

A well-defined track between skin and trachea does not form for 4 to 5 days after incision. Should the tube become displaced during this vulnerable period, the patient is placed at risk for life-threatening consequences. These include dyspnea, tracheal compression with asphyxia, hypoxemia, pneumothorax, pneumomediastinum, and secretion retention. Distortion and swelling of the subcutaneous tissues may prevent easy reentry of the same-sized tube through the skin wound. Through this hazardous period, the original tracheostomy tube must remain relatively undisturbed. Even placing a tracheostomy tube of smaller size can prove unsuccessful unless traction sutures that identify and spread the tracheal opening are in place. Traditional teaching suggests that oral intubation will be necessary in most of these emergent situations and should be undertaken immediately. Personal experience suggests, however, that an initial attempt to recannulate is prudent, as it is usually successful with the aid of stomal sutures.

**SUGGESTED READINGS**


Chapter 7
Elements of Invasive and Noninvasive Mechanical Ventilation

• Key Points

1. Prime indications for initiating mechanical ventilation include inadequate alveolar ventilation, inadequate airway protection, inadequate arterial oxygenation, excessive respiratory workload, and acute heart failure with labored breathing.

2. For machine-aided breathing cycles, the physician must determine the minimum frequency of the machine’s inspiratory cycling, the pressure or tidal volume, the inspired oxygen fraction, the triggering sensitivity, and the levels of certain boundary conditions (e.g., end-inspiratory, end-expiratory, and driving pressures, alarm limits).

3. Positive pressure inflation can be achieved with machines that control either of the two determinants of ventilating power—pressure or flow—and terminate inspiration according to pressure, flow, volume, or time criteria. Both pressure and flow cannot be fixed simultaneously because once either is set, the other becomes a dependent variable influenced by the interaction of the inflation mechanics with the controlled variable.

4. The fundamental difference between pressure-targeted and volume-targeted ventilation is implicit in their names. Strictly pressure-targeted modes regulate pressure at the expense of letting flow and tidal volume vary; volume-targeted modes guarantee flow and/or tidal volume but let airway pressure vary.

5. Standard modes of positive pressure ventilation include assist-control ventilation, SIMV, and PSV. The first two can be applied using either flow-controlled or pressure-controlled machine cycles.

6. Potentially useful ventilatory options include pressure-regulated volume control, automatic tube compensation, airway pressure release ventilation, biphasic airway pressure, adaptive support ventilation, proportional assist ventilation, and neurally adjusted ventilatory assist. Many of these innovations combine desirable features of pressure preset and flow-controlled, volume-targeted ventilation. The proper place of high-frequency oscillation for adults is unclear.

7. Certain adjuncts to mechanical ventilation, including permissive hypercapnia, neuromuscular blockade, prone positioning, and extrapulmonary gas exchange, are now widely applied in clinical practice. The value of other methods, such as inhaled nitric oxide, tracheal gas insufflation, and partial liquid ventilation remains unproved.

8. Noninvasive ventilation is particularly helpful when initiated early in the course of rapidly reversible diseases that respond to modest airway pressures and in the immediate postextubation period. Good examples are exacerbated COPD and congestive heart failure. It is less often successful for patients whose condition has already deteriorated, for patients who are comatose or noncooperative, and for patients who either cannot be attended closely or are hemodynamically unstable.

9. High-flow nasal oxygen is an attractive and well-tolerated option for patients who require minimal ventilatory support.

INDICATIONS FOR MECHANICAL VENTILATION

Decisions to institute mechanical support should be made independently of those made to perform tracheal intubation or to use positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP).
This is especially true considering the recently improved noninvasive (nasal high-flow and mask) options and interfaces for support. As ventilation with positive pressure assumes the work of breathing (WOB), potentially important changes occur in pleural pressure, ventilation distribution, and cardiac output (Fig. 7-1). Mechanical assistance may be needed because oxygenation cannot be achieved with an acceptable FiO₂ without manipulating PEEP, mean airway pressure, and pattern of ventilation, because a sedation requiring operation or procedure is needed, or because unchecked spontaneous ventilation places excessive demands on ventilatory muscles or on a compromised cardiovascular system (Table 7-1).

**FIGURE 7-1. Important physiologic differences between spontaneous and mechanical ventilation.** As the proportion of ventilatory support with positive pressure increases, WOB falls and pleural pressure rises, influencing venous return, left ventricular (LV) afterload, and ventilation/perfusion ([V with dot above]/[Q with dot above]) matching.

**Inadequate Alveolar Ventilation**

Apnea and deteriorating ventilation despite other therapeutic measures are absolute indications for mechanical breathing assistance. Usually, in such cases, there are signs of respiratory distress or advancing obtundation, and serial blood gas measurements show a falling pH and stable or rising PaCO₂. Although few physicians withhold mechanical assistance when the pH trends steadily downward and there are signs of physiologic intolerance, there is less agreement regarding the absolute values of PaCO₂ and pH that warrant such intervention; these clearly vary with the specific clinical setting. In fact, after intubation has been accomplished, pH and PaCO₂ may be allowed to drift deliberately outside the normal range to avoid the high ventilating pressures and tidal volumes that tend to induce lung damage (see Chapter 8). This strategy—permissive hypercapnia—is now considered integral to a lung-protective ventilatory approach for the acute management of severe asthma and acute respiratory distress syndrome (ARDS). Acute hypercapnia has well-known and potentially adverse physiologic consequences. Nonetheless, recent experimental work in varied models of clinical problems—notably, ischemia/reperfusion and ventilator-induced lung injury—clearly indicate that certain forms of cellular injury are actually attenuated by hypercapnia (ARDS; see Chapter 24).
Table 7-1. Indications for Mechanical Ventilation

| Inadequate ventilation to maintain pH |
| Inadequate oxygenation |
| Excessive breathing workload |
| Acute pulmonary edema |
| Shock states |

Blood pH is often a better indicator than PaCO$_2$ of the need for ventilatory support. Rate of rise is a key factor. Hypercapnia per se should not prompt aggressive intervention if pH remains acceptable and the patient remains alert, especially if CO$_2$ retention has occurred slowly and is not trending rapidly upward. Many patients require ventilatory assistance despite levels of alveolar ventilation that would be appropriate for normal resting metabolism. For example, patients with metabolic acidosis and neuromuscular weakness or airflow obstruction may lower PaCO$_2$ to 40 mm Hg or below but not sufficiently to prevent acidemia. The physiologic consequences of altered pH are still debated and clearly depend on the underlying pathophysiology and comorbidities. However, if not quickly reversible by simpler measures, a sustained pH greater than 7.60 or less than 7.10 is often considered sufficiently dangerous in itself to require control by mechanical ventilation and sedation (with muscle relaxants, if needed). Between these extremes, the threshold for initiating support varies with the clinical setting. For example, a lethargic patient with asthma who struggles to breathe can maintain a normal pH until shortly before suffering a respiratory arrest, whereas an alert cooperative patient with chronically blunted respiratory drive may allow pH to fall to 7.25 or lower before recovering uneventfully in response to aggressive bronchodilation, steroids, and supplemental oxygen. In less obvious situations, the decision to ventilate should be guided by trends in pH, arterial blood gases, mental status, dyspnea, hemodynamic stability, and response to therapy. The ongoing need for ventilatory assistance must be carefully and repeatedly assessed (see Chapter 10).

**Inadequate Oxygenation**

Arterial oxygenation is the result of complex interactions between systemic oxygen demand, cardiovascular adequacy, and the efficiency of pulmonary oxygen exchange. Improving cardiovascular performance and minimizing O$_2$ consumption (by reducing fever, agitation, pain, etc.) may dramatically improve the balance between delivery and consumption. Transpulmonary oxygen exchange can be aided by supplementing FiO$_2$, by using PEEP or changing the pattern of ventilation to increase mean airway (and consequently, mean alveolar) pressure and average lung size (see Chapter 5), or by prone positioning. In patients with edematous or injured lungs, relief of an excessive breathing workload may improve oxygenation by relaxing the expiratory muscles (improving end-expiratory lung distention) and by allowing the mixed venous O$_2$ saturation and venous admixture to improve.

Modest fractions of inspired oxygen are administered to nonintubated patients using masks or nasal cannulas. Controlled, low-to-moderate range O$_2$ therapy is best delivered to the nonintubated patient by a well-fitting Venturi mask, which allows for changes in inspiratory flow demand without significant change in delivered FiO$_2$. 
Without tracheal intubation or well performing non-invasive ventilation, delivery of high FiO₂ can only be achieved with a snug nonrebreathing mask that is flushed with high flows of pure O₂. Unfortunately, apart from the risk of O₂ toxicity, masks often become displaced or must be removed intentionally for eating, comfort, or expectoration. High-flow nasal oxygen may provide a good alternative in some cases of mask intolerance but cannot assure high FiO₂ or effective airway clearance. Intubation allows consistent and precise control of FiO₂, facilitates the application of PEEP and CPAP, and enables extraction of retained secretions from the central airways.

Although positive airway pressure (noninvasive ventilation [NIV] or CPAP) can be applied to spontaneously breathing, nonintubated patients, these techniques may not be well tolerated for extended periods, especially by confused, claustrophobic, poorly cooperative, or hemodynamically unstable patients who require high mask pressures (>15 cm H₂O; see “Noninvasive Ventilation,” following). Patients who need help to clear airway secretions also are poor candidates for NIV. Moreover, with the airway unprotected, these methods should be used only with extreme caution in patients who are obtunded or comatose. Positive airway pressure delivered continuously by mask is best tolerated at low levels for less than 48 hours, ideally with sporadic breaks allowed to relieve facial pressure.

**Excessive Respiratory Workload**

A common reason for mechanical assistance is a lack of ventilatory power or reserve. The respiratory muscles cannot sustain tidal pressures greater than 40% to 50% of their maximal isometric pressure. Respiratory pressure requirements rise with minute ventilation as well as with the impedance to breathing. Consequently, patients with hypermetabolism or metabolic acidosis often need ventilatory support to avoid respiratory decompensation. Impaired ventilatory drive or muscle strength further diminishes ventilatory capacity and reserve.

**Cardiovascular Support**

Although little effort is expended by normal subjects who breathe quietly, the O₂ demands of the respiratory system account for a high percentage of total body oxygen consumption (\(\dot{V}_{\text{O}_2}\)) during periods of physiologic stress (Fig. 7-2). Experimental animals in circulatory shock who receive mechanical ventilation survive longer than their unassisted counterparts. Moreover, patients with combined cardiorespiratory disease often fail attempts to withdraw ventilatory support for cardiac rather than respiratory reasons. Such observations demonstrate the importance of minimizing the ventilatory O₂ demand during cardiac insufficiency or ischemia. Doing so helps rebalance myocardial O₂ supply with requirements and/or allows diaphragmatic blood flow to be redirected to other O₂-deprived vital organs. Reducing ventilatory effort also may improve afterload to the left ventricle (see Chapter 1). Therefore, the physician should intervene early to relieve an excessive breathing workload for patients with compromised cardiac function. Although it is possible to use NIV or CPAP alone for mildly to moderately affected patients, fatigue often sets in unless underlying oxygen requirements are reduced substantially, which often requires adequate sedation or higher pressures than can be provided noninvasively.
FIGURE 7-2. Influence of ventilatory support on perfusion adequacy and oxygen consumed by ventilatory musculature. The work cost of spontaneous breathing and the increased afterload to LV ejection often contribute significantly to anaerobiosis and lactic acid production during circulatory shock. A better balance between oxygen delivery and consumption can be achieved when ventilation is controlled, thereby freeing needed oxygen for other organ systems. Conversely, boosting circulatory output in the setting of shock improves oxygen delivery to the fatiguing respiratory muscles, improving their $O_2$ supply and endurance.

OPTIONS IN MECHANICAL VENTILATION

Types of Ventilation

*Spontaneous Breathing Versus Ventilation with Positive Airway Pressure*

To accomplish ventilation, a pressure difference must be developed phasically across the passive lung. This difference can be generated by negative pressure developed by respiratory muscles in the pleural space, by positive pressure applied to the airway opening, or by a combination of both. (Although of major historical interest, negative pressure ventilators are very rarely appropriate for the modern acute care setting and will not be discussed.)

One potentially important difference between spontaneous and positive pressure breaths is that the pressure developed across the alveolus at any given volume during the process of spontaneous inflation not only must hold open the lung but also create the additional pressure gradient needed to pull inspiratory airflow across resistance through the airways. Flow demand contributes significantly to the spontaneous WOB (see Fig. 5-18 and Chapter 9).

*Regulating Flow or Pressure During Positive Pressure Ventilation*

When using positive pressure during machine-aided cycles, the physician must determine the machine’s minimum cycling rate, the duration of its inspiratory cycle, the baseline pressure (PEEP), and either the pressure to be applied or the tidal volume to administer, depending on the “mode” selected. Positive pressure inflation can be achieved with machines that control either of the two determinants of ventilating power—pressure or flow—
and terminate inspiration according to pressure, flow, volume, or time limits. Waveforms for both flow and pressure cannot be controlled simultaneously, however, because the mechanical energy needed to accomplish inflation is defined and constrained by physics (Fig. 7-3). During flow control, pressure is developed as a function of flow and the impedance to breathing, which is determined by the uncontrolled parameters of resistance and compliance. Thus, the clinician has the choice of specifying pressure, with flow as the resulting (dependent) variable, or of controlling flow, with pressure as the dependent variable. Whereas older ventilators offered only a single control variable and a single cycling criterion, positive pressure ventilators of the latest generation enable the physician to select freely among multiple options.

**Pressure-Cycled Ventilation**

Although pressure-cycled (pressure-limited) ventilators generally have been supplanted by more advanced machines that offer multiple modes with different cycling criteria (time or flow), some are still used, especially in economically depressed regions or developing countries. In their simplest form, these low-cost machines allow gas to flow continuously until a set pressure limit is reached. A pressurized gas source is all that is required to operate many of these machines, making them immune to electrical failure. Small size, portability, and low cost make this now obsolete equipment applicable for low-demand applications in transport and respiratory therapy.

**Pressure-Preset (Pressure-Targeted) Ventilation**

Modern ventilators provide pressure-preset or pressure-targeted ventilatory modes (e.g., pressure control or pressure support) as options for full or partial ventilatory assistance. After the breath is initiated, these modes quickly attain a targeted amount of pressure at the airway opening until either a specified time (pressure control) or a declining flow (pressure support) cycling criterion is met (Fig. 7-4). Maximal airway pressure is controlled, but tidal volume during passive inflation is a complex function of applied pressure and its rate of approach to
target pressure, available inspiratory time, and the impedance to breathing (compliance, inspiratory, and expiratory resistance, and auto-PEEP). Effort by the patient may add to the total pressure moving the lung. With its high-flow capacity, pressure-targeted ventilation compensates well for small air leaks and is therefore quite appropriate for use with leaking or uncuffed endotracheal (ET) tubes, as in neonatal or pediatric patients. Because of its virtually “unlimited” ability to deliver flow, pressure-targeted ventilation also is often an appropriate choice for some spontaneously breathing patients with high or varying inspiratory flow demands, which usually rise to the peak value early in the ventilatory cycle. The decelerating flow profiles of pressure-targeted modes also improve the distribution of ventilation in lungs with heterogeneous mechanical properties (widely varying time constants). Apart from their potential to limit the lung's exposure to high airway pressure and risk for barotrauma, pressure-targeted modes also prove helpful for adult patients in whom the airway cannot be completely sealed (e.g., bronchopleural fistula).

**FIGURE 7-4. Comparison of flow profiles during passive inflation by three time-cycled modes of ventilation.** Note that the flow-controlled decelerating flow tracing is regulated to decay linearly, whereas pressure-controlled ventilation is characterized by a die-away exponential curve.

**Flow-Controlled, Volume-Cycled Ventilation**

For many years, flow-controlled, volume-cycled ventilation (assist-control) has been the technique of choice for supporting seriously ill adult patients. Flow can be controlled by selecting a waveform (e.g., constant or decelerating) and setting a peak flow value or by selecting a flow waveform and setting the combination of tidal volume and inspiratory time. By controlling the tidal volume and “backup” frequency, a lower limit for minute ventilation can be guaranteed. Unfortunately, there are two important trade-offs of controlling flow. First, the pressure required to ventilate with any given PEEP and tidal volume varies widely with the impedance to breathing. High trans-lung pressures, however developed, may risk ventilator-induced lung injury (see Chapter 8). Moreover, once the peak and profile of flow are chosen, they remain relatively inflexible to increased (or decreased) inspiratory flow demands.

**Differences Between Pressure-Targeted and Volume-Targeted Ventilation**

After the decision has been made to initiate mechanical ventilation, the physician usually decides to use either pressure-controlled ventilation (PCV) or volume-cycled ventilation. For a well-monitored passively ventilated...
patient, pressure-targeted and volume-targeted modes can be used interchangeably with virtually identical benefit and risk. With either method, FiO\textsubscript{2}, PEEP, and backup frequency must be selected. If pressure control (sometimes referred to as pressure assist-control) is used, the targeted inspiratory pressure (above PEEP) and the inspiratory time must be selected (usually with consideration toward the desired tidal volume). Pressure support differs from pressure control in that each pressure-supported breath must be patient initiated (triggered). Furthermore, the expiratory trigger for pressure support is flow, rather than time, so that cycle length is free to vary with patient effort. If volume-cycled ventilation is used, the physician may select (depending on ventilator) either tidal volume and flow delivery pattern (waveform and peak flow) or flow delivery pattern and minimum minute ventilation (\(V_E\)), with tidal volume the resulting quotient of \(V_E\) and backup frequency.

The fundamental difference between pressure- and volume-targeted ventilation is implicit in their names; pressure-targeted modes guarantee pressure at the expense of letting tidal volume vary, and volume-targeted modes guarantee flow—and consequently the volume provided to the circuit in the allowed inspiratory time (tidal volume)—at the expense of letting airway pressure float. This distinction governs how they are used in clinical practice (Table 7-2). With both forms of ventilation, attention should be directed toward plateau pressure, PEEP, and their difference—the driving pressure.

Flow and tidal volume are important variables to monitor when pressure targeting, whereas airway pressure is of parallel importance in volume targeting. Gas stored under pressure in compressible circuit elements does not contribute to effective alveolar ventilation. For adult patients, such losses (approximately 2 to 4 mL/cm H\textsubscript{2}O of peak pressure) usually constitute a modest fraction of the tidal volume. For infants, however, compressible losses may comprise such a high fraction of the \(V_T\) that effective ventilation varies markedly with peak cycling pressure. Modern ventilators automatically take such factors into account.

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<th>Table 7-2. Pressure-Controlled Versus Volume-Controlled Ventilation</th>
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Volume-targeted modes deliver a preset volume unless a specified circuit pressure limit is exceeded. Major
advantages to volume targeting are the capacity to deliver unvarying tidal volumes (except in the presence of a
gas leak), flexibility of flow and volume adjustments, and power to ventilate difficult patients. Despite its
advantages for acute care, volume cycling also has important disadvantages. Unless the airway is well sealed,
volume-cycled modes may not ventilate effectively and consistently. Furthermore, after the flow rate and profile
are set, the inflation time of the machine remains fixed and unresponsive to the patient's native cycling rhythm
and flow demands. Just as importantly, excessive alveolar pressure may be required to deliver the desired tidal
volume. Pressure-targeted modes confer flexibility to flow demand and, when flow cycled, to cycle duration as
well.

**Standard Modes**

* Controlled Mechanical Ventilation*

With the sensitivity adjustment turned off during controlled mechanical ventilation (CMV), the machine provides a
fixed number of breaths per minute and remains totally uninfluenced by the patient's efforts to alter frequency.
This seldom used “lockout” mode demands constant vigilance to make appropriate adjustments for changes in
ventilatory requirements and is used only for situations in which pH and/or PaCO$_2$ must be controlled tightly
(e.g., some neurologic patients). Most patients require deep sedation to ablate breathing efforts. Under these
conditions, assist-control ventilation has similar capability and offers additional advantages (less patient-
ventilator asynchrony).

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**Assist-Control Ventilation**

During assist-control ventilation (or assisted mechanical ventilation [AMV]), each inspiration triggered by the
patient is powered by the ventilator using either volume-cycled or pressure-targeted breaths (Fig. 7-5). When
pressure is the targeted variable and inspiratory time is preset, the mode is known as pressure control or
pressure assist-control. Machine sensitivity to inspiratory effort can be adjusted to require a small or large
negative pressure deflection below the set level of end-expiratory pressure. Alternatively and more typically,
modern ventilators can be flow triggered, initiating a cycle when a flow deficit is sensed in the expiratory limb of
the circuit relative to the inspiratory limb during the exhalation period. A backup rate is set so that if the patient
does not initiate a breath within the number of seconds dictated by that frequency, a machine cycle begins
automatically. A backup rate set high enough to cause alkalosis blunts respiratory drive and terminates the
patient's efforts to breathe at the “apneic threshold” for PaCO$_2$. In awake, normal subjects, this threshold usually
is achieved when PaCO$_2$ is abruptly lowered to 28 to 32 mm Hg; it may be considerably higher during sleep or
when sedating drugs are given. Note that unlike CMV or synchronized intermittent mandatory ventilation (SIMV;
see following), changes in set machine frequency during AMV have no effect on $V_E$ unless this backup frequency
is set high enough to terminate the patient's own respiratory efforts.

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**FIGURE 7-5. Airway pressure waveforms characteristic of conventional modes of mechanical
ventilation.**
Synchronized Intermittent Mandatory Ventilation

During SIMV, the intubated patient is connected to a single circuit that allows both spontaneous breathing and a set number of mechanical cycles timed to coincide with inspiratory effort. Ventilator breaths—volume cycled or pressure controlled and usually larger than the spontaneous cycles—are interspersed to supplement spontaneous ventilation, which is usually pressure supported. Because SIMV can provide a wide range of ventilatory support, it can be used either as a full support mode or as a weaning mode, depending on the mandatory frequency selected. In recent years, SIMV has become much less popular as more attractive options are now available for most purposes.

Pressure-Support Ventilation

Description

Pressure support ventilation (PSV) is a method with which each breath taken by a spontaneously breathing patient receives a positive pressure boost set by the clinician. After the breath is initiated, airway pressure builds rapidly toward the inspiratory pressure target. Inspiratory airway pressure is then maintained constant at the clinician-set level until flow decays sufficiently to satisfy the machine’s “off-switch” criterion. At relatively slow respiratory rates, the resulting airway pressure profile resembles a “square” wave. Because PSV is flow cycled (and therefore influenced by pleural pressure), the patient retains control of cycle length and tidal volume. Modern ventilators allow the clinician to modify the aggressiveness with which the pressure target is approached as well as the flow off-switch criterion to span the full spectrum of patient mechanics and requirements. PSV provides the basis for a number of other ventilatory modes, such as SIMV and volume-assured pressure support (VAPS).

Advantages

PSV hybridizes the power of the machine and the patient, providing assistance that ranges from no support at all to almost fully powered ventilation, depending on the machine's developed pressure relative to patient effort. Because the depth, length, and flow profile of the breath are patient influenced, custom-adjusted PSV (with well-chosen amplitude, pressure ramp, and off-switch values) tends to be relatively comfortable in comparison with time-cycled modes. Adaptability to the vagaries of patient cycle length and effort can prove especially helpful for patients with erratic breathing patterns that otherwise would be difficult to adapt to a fixed flow or pressure profile accompanied by a set inspiratory time (e.g., COPD, anxiety). The transition to spontaneous breathing is eased by the gradual lowering of the pressure applied (see Chapter 10). Although PSV has its widest application as a weaning mode, it also is valuable in offsetting the resistive work required to breathe spontaneously through an ET tube, as during CPAP or SIMV. Another more sophisticated means for doing so, known as automatic tube compensation (ATC), offsets tube resistance by varying the applied pressure in proportion to flow. When used to support ventilation, the pressure support level should be adjusted to maintain adequate tidal volume at an acceptable frequency (<30 breaths/min). In theory, PSV would provide sufficient power for nearly the entire WOB if set to meet or exceed the average inspiratory pressure required per breath ($P_{req}$). For a normal subject breathing at a moderate rate, $P_{req}$ is amazingly small, seldom exceeding 7 cm H$_2$O. For patients who are appropriate for weaning, $[V \text{ with dot above}]_{E}$ usually approximates 10 L/min or less, and $P_{req}$ commonly does not exceed 10 to 15 cm H$_2$O. This helps explains why some patients seem to be “weaning smoothly” until some rather low threshold value of PSV is reached, at which point further reductions precipitate dyspnea.

Problems

PSV requires the ventilatory cycle to be patient initiated and does not adjust itself to changes in the ease or
difficulty of chest inflation. To draw more help from the machine, the patient often adjusts frequency to reduce effort. PSV is not an ideal mode for patients with unstable ventilatory drive or highly variable thoracic impedance (e.g., bronchospasm, copious secretions, or changing auto-PEEP). Appropriately set backup and apnea alarms improve safety under such circumstances. Because approximation of a true square wave of airway pressure deteriorates as ventilatory demands increase, the average inspiratory pressure (and tidal volume) resulting from PSV tend to be somewhat frequency sensitive.

**Ventilator Setup**

**Humidifier and Respiratory Circuit**

At the start of inspiration, the exhalation valve closes and airway pressure builds. PEEP is applied by causing the exhalation valve to close at a preset pressure level. Valves on older generation machines imposed substantial expiratory resistance, but modern “active” valves are quite efficient in this regard. Any extra tubing inserted between the ET tube and the Y-connector extends the “anatomic” dead space with that imposed by the apparatus, impairing ventilation efficiency.

With the normal upper airway bypassed, pressurized gas must be warmed and humidified before entering the trachea. (Humidification is also important when support is provided by a pressurized facemask [NIV], as many such patients inspire through the mouth, rather than through the nasal passages, and supplemental oxygen is inherently dry.) Disposable low-resistance heat and moisture exchangers (HMEs) or “artificial noses” connected directly between the Y-piece and endotracheal tube may be used for patients with modest ventilatory requirements and minimal airway secretions (e.g., in the postoperative setting). By recovering a high percentage of the exhaled water vapor, these units are able to satisfactorily humidify inspired gas for most patients. These devices impose a little dead space and may increase expiratory resistance, especially when saturated with liquid or contaminated by secretions. Consequently, a given unit performs less well when used for extended periods (>24 hours) or when provided to patients with copious airway secretions. With acceptable efficiency, low price, and less maintenance cost, HMEs have become the default humidifier choice in many intensive care units.

Another option, the “heated humidifier,” tends to perform better than an HME when thickened secretions are a problem. These humidifiers maintain a fairly consistent temperature throughout the external circuit, keeping water vapor in its gaseous phase. These are largely successful in keeping condensate from forming before the Y-connector. Because warmed, fully saturated gas cools in unheated connecting tubing, some condensation (“rain-out”) should occur in nonheated circuits. Using such equipment, a humidifier maladjustment or malfunction should be suspected if fine water droplets are not evident. The inspired temperature of fully saturated gas should be maintained at approximately 34°C to 36°C. If airway secretions are thick, the temperature should be raised to hydrate them (but not to exceed 37°C). Excessive rain-out may result in pooled liquid that can interfere with machine triggering or inadvertently empty into the lung during position changes, thereby injecting a bacterial inoculum or precipitating coughing or bronchospasm. Convincing studies indicate that frequent changes, disconnections, or manipulations of the external circuit increase the incidence of ventilator-associated pneumonia. Therefore, it is recommended to follow a circuit maintenance protocol in each intensive care unit.

**Inspired Oxygen Fraction (FiO₂)**

Initially, FiO₂ should be set to err deliberately on the high side, with later adjustment guided by arterial oximetry or blood gases. Immediately after intubation, for example, it is generally prudent to administer pure oxygen until adequate arterial oxygenation has been confirmed. Although adjustments of FiO₂ and PEEP are often made using the continuous output from a pulse oximeter, it should be considered that the sensitivity and accuracy of such instruments is frequently suboptimal. For continuing use, it is desirable to limit FiO₂ to 0.6 or less whenever
possible, with the objective of decreasing the risk of injury related to biochemically noxious reactive oxygen species. Arterial hyperoxia may encourage vasoconstriction and is to be avoided.

**Ventilator Options and Settings**

Major decisions in ventilator setup (Table 7-3) concern operating mode, FiO$_2$, tidal volume, guaranteed ventilator frequency, and baseline airway pressure (PEEP). Although minor adjustments can be made safely on the basis of vital signs, physical examination, subjective response, pulse oximetry and venous blood gases, initial choices and major setting adjustments should be verified by checking arterial blood gases drawn within 20 to 30 minutes of the change.

**Mode**

The pressure or volume assist-control modes generally are the best choices for full support because they allow the patient to control pH and PaCO$_2$ while the machine reliably powers inflation. Trigger sensitivity should be set at the lowest level that avoids excessive or auto cycling. It should be recognized, however, that effective triggering sensitivity is greatly reduced in the presence of dynamic hyperinflation (auto-PEEP). Encouraging spontaneous breathing has shown some benefits such as lower requirements for sedation, increased venous return and cardiac output, and improved ventilation/perfusion ratio. For these reasons, it seems prudent to promote *comfortable* spontaneous breathing from the onset of ventilatory support if the patient's clinical status permits.

<table>
<thead>
<tr>
<th>Table 7-3. Ventilator Setup</th>
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<tbody>
<tr>
<td>Mode</td>
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<tr>
<td>Backup frequency</td>
</tr>
<tr>
<td>PEEP</td>
</tr>
<tr>
<td>FiO$_2$</td>
</tr>
<tr>
<td>Target inspiratory pressure and time (pressure control)</td>
</tr>
<tr>
<td>Target tidal volume (volume control)</td>
</tr>
<tr>
<td>Inspiratory flow rate and wave shape (volume control)</td>
</tr>
<tr>
<td>Alarms</td>
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<tr>
<td>Apnea</td>
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<tr>
<td>Low exhaled tidal volume and/or $V_E$</td>
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<tr>
<td>Low inspiratory pressure</td>
</tr>
<tr>
<td>Maximum peak airway pressure</td>
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</tbody>
</table>

Compared to AMV, SIMV allows lower mean intrathoracic pressure, minimizing impedance to venous return. Currently, SIMV is almost always used with pressure support (or ATC) for spontaneous (non-time-cycled) breaths. With PSV applied, intermittent mandatory ventilation provides a useful alternative to sedation and control for patients who have difficulty synchronizing breathing rhythm with that of the ventilator during AMV or PCV, whose minute ventilation needs vary widely, or who require some mechanical assistance but hyperventilate inappropriately when allowed to trigger the machine on every cycle (e.g., central neurogenic hyperventilation, anxiety). Unless each nonmandated breath is supported with the same pressure used during pressure- or volume-targeted machine cycles, the patient's ventilatory workload of SIMV increases in proportion to the number
of spontaneous breaths taken.

CPAP alone may be appropriate for patients who comfortably maintain ventilation but require airway protection and/or improved arterial oxygenation (e.g., mild forms of ARDS). However, a low level of pressure support is usually added to overcome ET tube resistance.

OTHER VENTILATORY OPTIONS

Variation of the airway pressure baseline around which spontaneous efforts are made has spawned airway pressure release ventilation (APRV) and its variants (e.g., bilevel ventilation). APRV has implemented in some medical centers as a mode of first choice in treatment of ARDS, as it applies a relatively high mean airway pressure that prioritizes sustained recruitment of unstable alveoli and allows spontaneous efforts to continue. Its advantage, however, has yet to be convincingly shown (see Airway Pressure Release, following). In less severely ill patients, it is often desirable either to adjust midinspiratory flow in response to changing patient needs or, alternatively, to restrict maximal cycling pressure but ensure delivery of a specified tidal volume. In response, microprocessor capability has given rise to such “combination” modes as pressure-regulated volume control (PRVC) (also branded as autoflow or VC+), volume support (VSV), and volume-assured pressure support (VAPS) (Fig. 7-6). This group of modes is known as dual-control modes, because they allow the clinician to set a volume target as the ventilator delivers pressure-controlled breaths. Further steps in coordinating patient demand and machine flow response have been taken with proportional assist ventilation (PAV) and neurally adjusted ventilatory assist (NAVA) (see below).

PRESSURE-REGULATED VOLUME CONTROL

This mode satisfies a tidal volume with the least pressure control that accomplishes it within the preset inspiratory time. Pressure and inspiratory duration are continuously regulated in response to changing inflation impedance to satisfy the tidal volume objective. It should be noted that unlike pressure control, the patient may potentially receive no help at all from the ventilator if a satisfactory tidal volume is attained through patient effort alone.

VOLUME SUPPORT

In VSV, flow-cycled pressure support is adjusted up or down, depending on the tidal volume and minute ventilation that result in comparison with the preset minimums. Minute ventilation is the primary target variable, and a tidal volume minimum is guaranteed. When breathing frequency falls, tidal volume can increase by as much as 50% over the baseline target in an attempt to satisfy the \( \dot{V} \) minimum. Its advantages are to provide the positive attributes of PSV with assured levels of tidal volume and minute ventilation. Like PRVC, the ventilator's supporting pressure is an inverse function of breathing effort.

VOLUME-ASSURED PRESSURE SUPPORT

In VAPS, a fixed level of pressure support is aided by a backup flow generator if the PSV becomes insufficient to meet a minimum tidal volume objective. Thus, if lung compliance decreases or airway resistance increases, the set tidal volume is delivered by increasing the applied pressure (Fig. 7-6).

PROPORTIONAL-ASSISTED VENTILATION

Proportional-assisted ventilation was designed to increase or decrease airway pressure in direct relation to patient effort within the inflation period by amplifying airway pressure proportionally to inspiratory flow and volume. PAV is designed to adjust the amount of support it provides moment by moment in real time, in accordance with patient need. It was the first
mode to allow intracycle adjustment to muscular effort, while starting and stopping with precision. PAV does this by sensing flow demand and elastic counter-pressure, assisting ventilation to achieve a clinician-set work percentage that remains proportional to patient effort. Resistance and flow guide the pressure component supplied to overcome resistive forces, whereas elastance and inspired volume guide the pressure supplied to counterbalance elastic forces. Because these may frequently change, resistance and elastance are automatically estimated by stopping expiratory flow very briefly every 4 to 10 breaths. The overall amplitude of pressure assistance (a physician-set “work percentage”) can be varied by the caregiver from very low to high-level support (generally 20% to 80%). In effect, PAV acts as a powerful auxiliary muscle whose strength can be adjusted by the caregiver. It requires a backup (apnea) mode and settings in the event that the central drive is suppressed. Early problems with PAVs inherent insensitivity to auto-PEEP, circuit leaks, and “runaway” (overassisted) breaths have been largely addressed. Patient-ventilator synchrony is clearly better than with PSV, but despite its conceptual attractiveness, relatively few controlled trials convincingly demonstrate PAVs superiority over modern implementations of more traditional options that are set appropriately.

**FIGURE 7-6.** Conceptual representation of recently introduced modes of partial ventilatory support. In VSV, pressure support is automatically regulated to achieve preset targets for minimum tidal volume and minute ventilation. In VAPS (also known as pressure augmentation), a fixed pressure-support level may be augmented by constant flow at end inspiration, if necessary to achieve a preselected tidal volume target. Proportional assist ventilation increases the pressure output of the ventilator parallel to the vigor of patient effort, thereby acting as an auxiliary set of ventilatory muscles, the strength of which is regulated by the clinician. \( P_{aw} \), airway pressure; \( P_{es} \), pleural (esophageal) pressure.
NEURALLY ADJUSTED VENTILATORY ASSIST

The ideal of using the patient's own respiratory center nerve traffic to regulate the intensity of machine's output has been brought closer to reality by using the conditioned, integrated electromyographic (EMG) signal from the phrenic nerve to control machine's flow output on a moment-by-moment basis (Fig. 7-7). A purpose-designed esophageal catheter is required to capture the required diaphragmatic EMG signal, which of itself is a helpful indicator of respiratory drive. Whether the respiratory system controller of the diseased patient is a reliable, appropriate, and safe governor for machine output is a question being actively investigated. By sidestepping the need to measure flows and mechanics, NAVA effectively accounts for auto-PEEP and circuit leaks. Like PAV, NAVA appears to effectively address patient-ventilator asynchrony. Although initial clinical experience with this conceptually appealing method has been quite positive, NAVA's practical advantages over optimized routine modes are still being explored and must be considered unconfirmed.

FIGURE 7-7. Principle of neurally regulated ventilatory assist (NAVA). The conditioned EMG signal from the diaphragm regulates the shape and amplitude of the inspiratory airway pressure.

AUTOMATIC TUBE COMPENSATION

ATC compensates for ET tube resistance via closed-loop control of calculated tracheal pressure. In other words, ATC is similar to PSV, but the pressure applied by the ventilator varies as a function of ET tube resistance and flow demand. The proposed advantages of ATC are (1) to overcome the WOB imposed by the artificial airway, (2) to improve patient-ventilator power synchrony by varying flow commensurate with demand, and (3) to reduce air trapping by compensating for imposed expiratory resistance. Most of the interest in ATC revolves around eliminating the imposed WOB during inspiration. However, during expiration, there is also a flow-dependent pressure drop across the ET tube. ATC may also compensate for that flow resistance by lowering the pressure in the expiratory circuit limb transiently from its PEEP setting, helping reduce effective expiratory resistance and unintentional hyperinflation. ATC added to PSV may increase the tidal volume substantially.

Tidal Volume

Inspired tidal volume can either be a preset (controlled) parameter or a dependent variable that is taken into account when selecting the airway pressures during pressure-targeted ventilation. For otherwise healthy individuals, relatively large tidal volumes can be given without generating high pressures and may, in fact, be
necessary for adequate patient comfort. On occasion, tidal volumes higher than 10 mL/kg may be needed to satisfy the demands of a hyperpneic subject with normal ventilatory mechanics. A good starting value for most critically ill patients, however, is 6 to 8 mL/kg of predicted (not actual) body weight (PBW), provided that plateau pressure measured during passive inflation does not rise above 30 cm H\textsubscript{2}O. The tidal volume delivered to a patient with a reduced number of aeratable lung units must be reduced accordingly (e.g., ARDS, pneumonectomy, interstitial fibrosis). Monotonous shallow breaths (<5 mL/kg IBW) encourage microatelectasis unless interrupted periodically by larger inflations or offset by PEEP. If very small tidal volumes and low levels of PEEP are in use, one or more large breaths (sighs generally 1.5 to 2.5 times the $V_T$) per minute may be advisable to avert problems, but this point is controversial. As pressure builds during inspiration, a fraction of the inspired gas is stored in tubing and other compressible elements of the ventilator circuit (internal reservoirs, filters, humidifiers, etc.). Most modern equipment automatically adjusts for the circuit compression losses.

Measurements of exhaled volume potentially include compressible volume because tubing contracts during expiratory decompression. Again, most modern ventilators compensate for compressible volume on their digitized readouts. Under conditions of controlled ventilation, the discrepancy between set or measured inspiratory tidal volume and exhaled tidal volume can quantitate the severity of a bronchopleural fistula or of the leak past a deflated endotracheal tube cuff.

**Frequency**

In time-cycled modes of assisted ventilation, the backup frequency should be chosen in conjunction with $V_T$ or pressure setting to provide minute ventilation ($[\dot{V} with dot above]_E$) adequate to maintain pH and patient comfort. In the assist mode, this backup rate should be adjusted to a frequency sufficient to provide 70% to 80% of the patient's usual $[\dot{V} with dot above]_E$, in case of complete failure of the patient to trigger. In the AMV mode, any adjustments in the set frequency—up or down—have no effect on $[\dot{V} with dot above]_E$ or on the level of machine support, so long as the patient triggers each breath.

**Other Settings**

Flow-controlled, volume-cycled ventilators allow the physician to choose the inspiratory flow rate and to define its contour (square or decelerating). Inappropriately rapid inspiratory flow rates may worsen the distribution of ventilation in some patients; however, a decelerating flow waveform helps satisfy rapid early inspiratory flow demand. Although peak pressure rises as flow rate increases, the mean airway pressure averaged over the entire ventilatory cycle may remain unchanged or even fall as flow rate increases. The extent to which the ventilator takes up the inspiratory WOB is a function of the margin by which flow delivery exceeds flow demand. It is mandatory that the flow metered by the ventilator meets or exceeds the patient's flow demand throughout inspiration. Should airway pressure approach or even fall below its PEEP baseline, the ventilator not only fails to reduce the WOB but also forces the patient to pull against the resistance of the endotracheal tube and ventilator circuitry, as well as overcome internal impedance to airflow and chest expansion.

Comfortably rapid inspiratory flow rates also are desirable during AMV to ensure that the machine completes inflation before the patient's own ventilatory rhythm cycles into its exhalation phase. Delayed opening of the exhalation valve causes the patient to "fight" or "pressure limit" the ventilator. When the ventilator pressure limits, the full tidal volume is not delivered but vented to atmosphere. As a rule, to achieve a 1:3 inspiration-to-expiration ratio during flow-controlled assist-control, the ventilator's average inspiratory flow should be approximately 4.0 times the minute ventilation during quiet breathing. (If a different I:E is desired, then three times $V_E$ for 1:2 and twice $V_E$ for 1:1.) When ventilation demands are high, a longer I:E may be appropriate. (As $V_E$ demands
increase, and the flow setting is not readjusted, the I:E ratio automatically shortens with increasing frequency, as it does during natural breathing.) Peak flow should be set 25% to 35% higher than this average value when the decelerating waveform is used. Peak airway pressure is influenced by inspiratory flow rate and waveform, airway resistance, tidal volume, and total thoracic compliance. During an end-inspiratory pause, the plateau airway pressure reflects the maximum stretching force applied to a typical alveolus and surrounding chest wall. To avoid barotrauma, maximum pressure (alarm and “pop-off” pressure) should be set to no more than 15 cm H₂O above the peak dynamic cycling pressure observed during a typical breath during constant flow. The pop-off alarm should be set more closely than this (within 10 cm H₂O) if a decelerating flow waveform or pressure control is used because under those conditions, end-inspiratory dynamic and static (plateau) pressures are not as widely separated.

When the patient is passive, the inflation hold setting allows for calculation of respiratory system compliance, estimates maximum alveolar pressure, and, when constant flow is in use, allows determination of resistance as well (see Chapter 5). A temporary inflation hold also can be used to check for circuit leaks, as circuit pressure will continue to decline during the pause interval rather than “plateau” as gas bleeds off.

Pressure control requires selection of the pressure target and inspiratory time, inspiratory time percentage, or the ratio of inspiratory-to-expiratory time—the I:E ratio. (In volume-cycled ventilation, the I:E ratio usually is set indirectly by specifying inhaled volume, frequency, and inspiratory flow.) In general, shorter I:E ratios allow more time for exhalation and reduce mean intrathoracic pressure. To avoid gas trapping, many ventilators provide a visual warning or auditory alarm when the I:E ratio exceeds 1:1 (duty cycle >0.5). This threshold defines inverse ratio ventilation (IRV).

### Innovative Modes to Improve Ventilation

The primary purposes of mechanical ventilation are to achieve adequate alveolar ventilation, to relieve an excessive breathing workload, and to improve oxygen exchange. For decades, the mainstays of ventilator assistance have been flow-controlled (“volume-controlled”) ventilation or AMV, PCV, PSV, and PSV combined with either PCV or AMV as SIMV. Similarly, enrichment of FiO₂ and the addition of end-expiratory pressure (PEEP, CPAP) remain the primary means of supporting oxygenation. Over the years, other interesting techniques have been developed, and a generous handful has now gained traction in clinical practice. These innovations take the form of newer modes of ventilation or of adjuncts to ventilatory support. Several designed for better interfacing with the patient making breathing effort are outlined in the section on “Mode” above. Each has a defensible physiologic rationale but little objective supporting data to document clinical benefit.

One interesting approach, adaptive support ventilation (ASV), uses is conventional ventilation but attempts to modify not only the pressure applied during pressure-controlled SIMV but also the frequency of delivered machine breaths to adapt to changing patient needs. The machine algorithm is guided by the breathing frequency, the depth of the breath, and the estimated WOB. By adjusting backup frequency and magnitude of pressure applied, the breathing pattern is made to lie within a hypothetical ideal “zone”—sufficient ventilation with pressure not too high, frequency not too high, and breathing workload optimized according to the “equation of motion” for the respiratory system (see Chapter 5). In a sense, like PAV and NAVA, this mode is geared to the breathing pattern—not micro managing within the breath to coordinate with patient effort as they do, but keeping the pattern consistent with the clinician’s clinical goals under changing conditions of requirement, demand, and mechanics.

### Nontraditional Modes to Improve Oxygenation

**High-Frequency Ventilation**
The collective term “high-frequency ventilation” (HFV) refers to methods of ventilation that intentionally depart from the breathing patterns encountered in spontaneous breathing. In various iterations of HFV tidal volumes that are routinely less than or equal to the calculated anatomic dead space are moved at frequencies as high as 3,000 cycles/min. The primary intent is to treat the lung gently and avoid using damaging excursions of alveolar pressure. The mechanisms by which these varied forms of HFV establish alveolar ventilation is uncertain and differs among techniques. Mean alveolar pressures may not differ greatly from—or even exceed—those observed during conventional ventilation of similar effectiveness. Although several variants of HFV (high-frequency positive pressure ventilation and jet ventilation) are of considerable historical significance, high-frequency oscillation (HFO) has garnered most recent attention for ICU applications.

**High-Frequency Oscillation**

During HFO, a very small tidal volume (1 to 3 mL/kg) is moved to and fro by a piston membrane at extremely high frequencies (300 to 3,000 cycles/min). Fresh gas is introduced as a continuous flow, and a narrow-gauge venting tube (a “low-pass filter”) provides egress for waste gas. Delivered tidal volume is determined by the machine’s “driving” pressure (not the same as that defined during conventional ventilation as $P_{\text{pl}}$—PEEP). Carbon dioxide elimination is a function of stroke (tidal) volume and paradoxically to the inverse of vibration frequency. Unlike jet ventilation, both phases of the ventilatory cycle are controlled actively by the oscillator's piston. Consequently, auto-PEEP less frequently poses a serious problem. Although fresh gas must be provided through the airway, pulsatility of the air column may originate either in the airway or at the lung surface. In experimental animals, mere vibration of the chest wall has successfully maintained marginal gas exchange. Although improved gas mixing and facilitated diffusion are undoubtedly important, pulsatility itself does not seem to be a strict requirement for some alveolar ventilation to occur. A continuous stream of $O_2$ introduced just beyond the carina can maintain arterial oxygenation and accomplish significant $CO_2$ washout in apneic animals, a technique dubbed “apneic diffusion,” “continuous flow apneic ventilation,” or “tracheal insufflation of oxygen” (TRIO). Although not advocated for clinical use, apneic ventilation may theoretically aid as a temporizing measure in emergent settings in which standard ET intubation cannot be quickly accomplished.

**Applications of High-Frequency Ventilation**

HFO has been widely adopted in neonatal management, but three decades after its introduction to practice, HFV still struggles to find its clinical niche in adult ICU care. HFV and the level of sedation needed to accomplish it can silence the normal respiratory rhythm and phasic tidal variations of chest volume. Because HFV does not require a cuffed ET tube, it has been helpful in bronchoscopy and laryngeal surgery. HFV occasionally is effective in the setting of bronchopleural fistulas that are refractory to closure, in part because of lower peak airway pressures. Fistulas also tend to draw less flow at higher frequencies because the inertance of the fistulous pathway is greater than that of alternative routes. Because high airway cycling pressures may be instrumental in causing airway and parenchymal forms of ventilator-induced lung injury, HFV may have a role in preventing these complications in neonates and perhaps in older children and adults with ARDS as well. HFO has been reported to compare favorably to conventional therapy in patients with acute lung injury in some studies, presumably because its relatively low driving pressure and relatively high end-expiratory and mean pressures apply an “open lung, lung-protective” approach. But safety depends on the range of mean airway pressure in which it operates, and one large and well-executed trial for acute respiratory failure reported impressively adverse results. It remains debatable whether any HFV technique holds an advantage over lung-protective approaches using conventional ventilators set to deliver modest tidal volumes and driving pressures with adequate PEEP. Some patients with high ventilation requirements or high thoracic impedance cannot be ventilated successfully by HFV. Other problems concern monitoring (a vexing clinical problem during HFV), high
noise level, and needs for deep sedation and the near continuous bedside presence of a trained operator.

**FIGURE 7-8.** Airway pressure waveforms corresponding to IRV, APRV, and biphasic airway pressure (BIPAP). In IRV, the airway is pressurized for more than one half of the total cycle length, increasing mean airway pressure. Deep sedation (with or without muscle relaxants) may be necessary to suppress spontaneous breathing efforts. APRV allows the patient to breathe spontaneously around an elevated pressure baseline, which is periodically released and reestablished, thereby aiding spontaneous ventilation. BIPAP extends the release cycle, allowing spontaneous ventilation to occur at each of the two CPAP levels.

**Pressure-Controlled Inverse Ratio Ventilation**

**Description and Rationale**

To prevent gas trapping, it has long been standard practice to allow at least as much time for exhalation as for inhalation; however, for certain patients with impaired oxygenation, gas exchange may improve when the I:E ratio is extended to values greater than 1:1 (Fig. 7-8). Inversion of the ratio prevents the patient from initiating or expelling a breath during the lengthy inspiratory period. IRV appears to offer no consistent advantage over conventional patterns that achieve similar levels of mean and end-expiratory alveolar pressures and is now seldom used. Occasionally, it may be worth considering when dangerously high plateau pressures would otherwise be required. It is now used only as a technique of last resort in cases of ARDS, even though IRV is most rational and seems to be most effective in the earliest phase, when lung units are most recruitable. At usual frequencies, inverse ratios greater than 2:1 are seldom helpful and may be dangerous. IRV should seldom be used for longer than 48 to 72 hours before reassessing its relative advantage over conventional ratio ventilation. IRV is not an appropriate mode of treatment for severely obstructed patients.

When using IRV, a pressure control waveform has the distinct advantage of safety when compared with flow-controlled, volume-cycled methods that leave alveolar pressure unregulated. IRV requires a passive patient, so deep sedation and/or paralysis usually are necessary. With breathing effort silenced, adequate circulating volume is required so as to avoid the hemodynamic consequences of its high mean airway pressure.

**Airway Pressure Release and Biphasic Pressure**

APRV and biphasic airway pressure (BIPAP) can be thought of as variants of IRV intended for use by spontaneously breathing patients in acute respiratory failure (Figs. 7-8 and 7-9). In this context, BIPAP should not be confused commercially termed “Bi-Pap,” a mode designed primarily for NIV and virtually synonymous with pressure support with or without added CPAP. The idea behind APRV is to provide added ventilatory support for a patient who needs high levels of CPAP for oxygenation but who can provide some of the ventilatory power requirement without machine assistance. Both APRV and BIPAP allow ventilatory efforts to occur around an
elevated pressure baseline (CPAP or $P_{\text{high}}$) over a set time period (time high) but also depressurize the system (partially or completely) to a lower pressure baseline for brief periods (time low) at a frequency set by the physician. After release, fresh gas enters as CPAP rebuilds to its higher value, improving ventilation. With APRV, the original idea was to keep release time very short—about one deflation time constant, rebuilding to the higher pressure level before lung collapse occurs (deliberate auto-PEEP). PEEP can be added, but this detracts from the driving pressure of release cycles. BIPAP differs from APRV primarily in allowing the option for extended periods of spontaneous breathing at both selected levels of end-expiratory pressure. Typically, APRV has a release time of about 0.8 seconds—well within a single partial deflation during the transient circuit decompression, whereas BIPAP allows for an extended time at the lower pressure baseline. Weaning occurs by dropping the high pressure and diminishing the number of release cycles. As commercially implemented, pressure support can be added to the spontaneous breaths that occur on either pressure baseline.

**Advantages**

These “open circuit” techniques can be viewed as methods to aid in ventilation and/or to elevate airway pressure to keep an “open lung” so as to better protect it and improve oxygenation. Phasic release cycles function in a manner similar to the machine cycles of SIMV, insofar as they augment the patient’s own ventilation. The difference is that high peak airway pressures generated with a closed expiratory valve are avoided, and spontaneous breathing can occur at any time. Patient-ventilator synchrony is generally well maintained. In theory, during inspiratory efforts, the total transalveolar pressure may be considerably greater than the upper APRV or BIPAP baseline. As with IRV, sustained higher airway pressure exerts prolonged traction on the lung, increasing global strain but improving recruitment. Unlike IRV, however, the patient remains conscious and can adjust alveolar ventilation to the extent that he or she is able to do so, often aided by pressure support. At least one prospective trial of APRV versus conventional lung-protective ventilation has reported quicker withdrawal of ventilator support with APRV use, attributable in part to lower sedation requirements. APRV places a premium on avoiding end-expiratory alveolar collapse, thought by many to be a key to lung-protective ventilation of ARDS. BIPAP (unlike APRV, which eventually requires a conversion to conventional ventilation as weaning proceeds) can provide the entire range of ventilatory support (ranging from completely controlled ventilation to unsupported breathing), depending on the difference between pressure baselines and the frequency and duration of the release cycles. For this reason, it serves as the primary platform for ventilatory support in at least one modern ventilator system.

**Disadvantages**

The efficacy of the pressure-release cycles in accomplishing ventilation depends on (1) the duration of release,
(2) the mechanical properties of the chest, (3) the difference between the two pressure baselines, and (4) the cycling frequency. In BIPAP, the transition between $P_{\text{low}}$ and $P_{\text{high}}$ represents a driving pressure that may exceed prudent values. As ventilation support increases, mean airway pressure falls, dissipating some of the oxygen-exchange benefit of the higher CPAP level. More importantly, the value of these modes is questionable for patients with significant airflow obstruction or severely reduced lung compliance. In the first instance, the brief release cycles of APRV are relatively ineffectual because of delayed lung decompression. In the second instance, the work of spontaneous breathing may be too great to sustain. Some concern has been raised that like all pressure-targeted modes, excessive transalveolar pressures might be generated during vigorous efforts made on the high-pressure baseline. Although certainly a potential problem, in practice, observational studies have shown this unlikely to occur on a routine basis. Although APRV and BIPAP need more studies to firmly establish their clinical indications, they are used increasingly—especially in the care of patients with acute lung injury and ARDS.

**Adjuncts to Mechanical Ventilation**

**Techniques to Improve Gas Exchange**

There has been sustained interest in developing techniques capable of maintaining or improving pulmonary gas exchange without the need to elevate alveolar and pleural pressures (Table 7-4). Such methods include the administration of therapeutic gases or aerosols (e.g., heliox, nitric oxide, and inhaled prostacyclin), alterations of body position (prone repositioning), dead space bypass or washout (intratracheal pulmonary ventilation, tracheal gas insufflation), and extrapulmonary gas exchange (extracorporeal membrane oxygenation and extracorporeal CO$_2$ removal). Some, like the passive arteriovenous and pump-driven venovenous circuits seem to hold genuine potential to improve the care of patients with life-threatening respiratory failure. Several of these techniques (e.g., prone positioning and extracorporeal gas exchange) are discussed elsewhere in this volume (see Chapters 8, 24, and 25). Perhaps the most effective and important "adjuncts" to ventilation simply relax the targets for pulmonary gas exchange when the physiology is severely compromised.

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<th>Table 7-4. Adjuncts to Mechanical Ventilation</th>
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<tr>
<td>Nitric oxide/inhaled prostacyclin</td>
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<tr>
<td>Vibration of airway or chest wall</td>
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<tr>
<td>Tracheal gas insufflation</td>
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<tr>
<td>Extrapulmonary gas exchange (ECMO)</td>
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<tr>
<td>Permissive hypercapnia</td>
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<td>Prone positioning</td>
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**Permissive Hypercapnia**

Permissive hypercapnia is a widely implemented ventilatory strategy that assigns higher priority to avoiding injurious pressures than to maintaining normal levels of alveolar ventilation. Allowing PaCO$_2$ to rise above baseline values is perhaps the simplest technique for reducing the ventilatory workload, the pressure cost of breathing, and/or the total number of machine cycles needed per minute. As PaCO$_2$ rises, each exhaled breath of a given volume eliminates more CO$_2$ than it would during normocapnia, thereby improving CO$_2$ excretion.
efficiency (Fig. 7-10). With reduced ventilation requirements, smaller tidal volumes can be delivered, lowering the peak and mean inflation pressures and, consequently, the work of spontaneous breathing. Because ventilatory power is a nonlinear function of $V_E$, small reductions in $V_E$ can reduce effort and transpulmonary pressure impressively (see Chapter 24).

![Diagram of PaCO$_2$ vs. alveolar ventilation](image)

**FIGURE 7-10. Relationship of PaCO$_2$ to alveolar ventilation ($V_{ALV}$).** Because this relationship is curvilinear, relatively small changes in $V_{ALV}$ that occur at low levels of ventilation have a dramatic effect on PaCO$_2$. An increase in CO$_2$ production ($\dot{V}_{CO_2}$) results in a higher PaCO$_2$ for any specified level of ventilation.

**Permissive Hypoxemia**

Renewed interest has also developed in slowly conditioning the hypoxemic patient to adapt to that abnormal state, rather than to compensate for it with potentially noxious therapies such as high FiO$_2$ and elevated mean airway pressures. Without question, healthy patients have an impressive ability to adapt gradually to environmental hypoxemia. However, the extent to which the patient with critical illness can safely do so and the appropriate schedule for implementing adaptation are unknown. Emerging options for monitoring adequacy of
tissue oxygenation and for carefully regulating FiO\textsubscript{2} will help in the titration process. It stands to reason that patients with ample hemodynamic reserve as well as near-normal levels of circulating volume and hemoglobin represent better candidates for such an experimental approach. Recently reported adverse experience with this technique in premature neonates suggests the need for vigilance and caution. Current experience with permissive hypoxemia in adults is insufficient to set firm indications, contraindications, and definitive boundaries.

![Figure 7-11. Varied interfaces with which to apply noninvasive ventilatory support.](image)

**Noninvasive Ventilation**

Many patients require only modest pressures to maintain compensated ventilation. With the increasing availability of improved interfaces and efficient valving mechanisms, the attractive option of applying ventilatory support without airway intubation by occlusive mask has become widely exercised—both for chronic nocturnal support and increasingly for acute in-hospital applications (Fig. 7-11). NIV may be used to quickly apply (and remove) ventilatory assistance without the risk and discomfort of intubation. Infection risk is considerably lower with NIV than in those who are intubated. Such attractive characteristics have numerous applications in emergency centers as well as in-hospital intensive and subacute settings, especially now that much improved, relatively comfortable mask interfaces are available. For example, NIV may sometimes provide a bridge across the treacherous postextubation period in marginally compensated patients recently weaned from ventilatory support. NIV allows communication and, when the mask is temporarily removed, effective expectoration, and eating. There is no major penalty for starting and stopping ventilatory support—
indeed, brief intervals off the mask every several hours may help improve tolerance. When prolonged near-
continuous NIV application is necessary, rotation among different interfaces or high-flow nasal cannula (see
following) should be considered.

Noninvasive methods are often helpful for patients who are not candidates for intubation (e.g., patients with
advanced directives not to intubate). For well-selected patients, noninvasive techniques may obviate the need
for intubation altogether and help avoid infections and other complications of securing the airway. A few centers
report improved mortality rates for selected categories of patients who are able to accept this treatment (e.g.,
exacerbated COPD). NIV seems to be particularly helpful when implemented at an early stage for noncomatose
patients with rapidly reversible diseases (e.g., congestive heart failure, exacerbated chronic airflow obstruction,
moderate asthma, transient upper airway obstruction) and for patients for whom intubation is not an acceptable
option. The interface chosen for this acute setting almost exclusively covers both nose and mouth (full face
mask). The worth of NIV for patients with acute pulmonary edema (especially of the “flash” variety) is now
proved. NIV should be considered strongly in mild-moderate cardiorespiratory failure and for those patients with
neuromuscular weakness, nocturnal hypoxemia, or hypoventilation. NIV can facilitate the extubation of COPD
patients intubated for hypercapnic ARF; however, as for all instances where NIV is used as an alternative to
invasive ventilation, this application requires an ICU team highly experienced with this technique. In patients at
high risk of extubation failure, NIV soon after planned extubation reduces the rate of reintubation and improves
overall outcomes. NIV reduces the rate of respiratory complications including reintubation in patients after high-
risk surgeries and chest trauma.

Timing of NIV administration is also important. Early NIV may be used to prevent the occurrence of overt
respiratory failure and avert the need for endotracheal intubation as other measures address the precipitating
cause. Patient selection is crucial, aiming to avoid patients at excessive risk of NIV failure. In patients at high risk
of extubation failure, NIV soon after planned extubation reduces the rate of reintubation and improves overall
outcomes.

For marginally compensated patients, noninvasive techniques may prove especially helpful at night, when sleep
impairs ventilatory drive or the REM phase immobilizes the nondiaphragmatic musculature crucial to maintaining
adequate ventilation. Indeed, nocturnal nasal ventilation (by nasal mask or other occlusive fitting) seems to be
useful over extended periods for selected patients with irreversible neuromuscular disease, sleep apnea, and
airflow obstruction. Intermittent rest of fatigued respiratory muscles and, in a minority of cases, improved lung
compliance may result. The precise reason for nocturnal NIV's lingering benefit during waking hours remains
undetermined. It has been suggested that nocturnal support may allow the sleep quality needed to preserve
adequate ventilatory drive and muscle strength. This is of particular interest in the ICU environment, where sleep
architecture is highly disorganized.

Despite its clear value for well-selected patients, NIV has important limitations as well (Table 7-5). NIV helps less
consistently in acute parenchymal
lung disease (e.g., ARDS), particularly when the ventilatory problem is far advanced, slowly evolving, or
unexpected to resolve quickly. Combative or comatose patients, those who cannot be attended or monitored
closely, and those with copious secretions, coronary ischemia, or super obesity are decidedly poor candidates.
Use of NIV in de novo hypoxemic respiratory failure, in particular those with moderate to severe ARDS, is
presently not advisable.

Table 7-5. Noninvasive Ventilation by Mask: Benefits and Limitations
### Benefits

<table>
<thead>
<tr>
<th>Easy to implement and remove</th>
<th>Claustrophobia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improves comfort</td>
<td>Hypoxemia when abruptly removed</td>
</tr>
<tr>
<td>Reduces need for sedation</td>
<td>Eye irritation</td>
</tr>
<tr>
<td>Preserves speech/swallowing</td>
<td>Difficult airway hygiene</td>
</tr>
<tr>
<td>Preserves cough</td>
<td>No airway protection</td>
</tr>
<tr>
<td>Avoids tube resistance</td>
<td>Facial discomfort and skin trauma</td>
</tr>
<tr>
<td>Avoids tube complications</td>
<td>Gastric distention</td>
</tr>
<tr>
<td>Upper airway trauma</td>
<td>Limited ventilatory capability</td>
</tr>
<tr>
<td>“Mini” aspiration</td>
<td></td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td></td>
</tr>
</tbody>
</table>

**Dilates upper airway**

### Limitations

- Hypoxemia when abruptly removed
- Eye irritation
- Difficult airway hygiene
- No airway protection
- Facial discomfort and skin trauma
- Gastric distention
- Limited ventilatory capability

However, NIV often is successful when applied early enough to cooperative patients with reversible disease by vigilant, well-trained personnel. A dedicated team approach has been shown highly effective. Gastric distention is unusual at peak mask pressures lower than 20 cm H$_2$O. Although skin irritation, nasal congestion, sinus discomfort, impeded expectoration, secretion thickening, sleep disruption, and claustrophobia are often troublesome, perhaps the greatest logistical problem continues to be mask leaks, which can develop quickly. These not only compromise ventilation and promote asynchrony but also place oxygen or PEEP-dependent patients at risk for hypoxemia and its sequelae. Importantly, leaks are better compensated when the ventilator has software purpose designed for NIV. Recent developments in mask technology have dramatically improved the range, quality, and comfort of mask interfaces. The need to maintain the patient arousable can limit the application of sedatives and analgesics. In some hospitals, the burgeoning use of NIV, combined with the need for specialized surveillance, has given rise to nursing units specializing in this modality.

Considering the many factors that potentially may influence the effectiveness of NIV, perhaps it is not surprising that experience and enthusiasm for this technique vary widely across centers. Apart from patient selection, among the most important elements of success with NIV are rigorous training of support personnel, early intervention, and dedicated efforts to coax and encourage the patient to accept NIV in the first few hours of its application. As a rule, attempts to make NIV work should not persist longer than 1 to 2 hours without clear evidence for benefit and tolerance, as lengthy delays in intubation risk adverse outcomes.

Except when patients are chronically receiving NIV at home, devices intended for chronic nocturnal prophylaxis against the upper airway obstruction of sleep apnea are not optimal for applications in the acute arena. Modern NIV equipment intended for inpatient support can provide well-hydrated inspired gas with precisely adjusted FiO$_2$, minimal CO$_2$ rebreathing, appropriate respiratory monitoring, and good sensitivity to patient cycling rhythm and flow demand. The best units are also appropriately alarmed. Although still imperfect regarding accuracy, the current ability of modern units to monitor delivered tidal volume, minute ventilation, and leak magnitude greatly assist the caregiver in adjusting the applied mask pressures. It should be noted that when dead space is minimized by reducing the tubing length between the Y-piece and a low-volume mask (similar to that used in bag-mask resuscitation equipment), a modern pressure targeting ICU ventilator can be effectively used (albeit suboptimally) in NIV applications.

Generally speaking, NIV is applied with a combination of a modified pressure support and CPAP across a pressure range of 0 to 25 cm H$_2$O. Higher pressures are very poorly tolerated and raise the risk for
complications. In common parlance, NIV of this type is often referred to as Bi-Pap, with the inspiratory pressure (sum of pressure support and CPAP) termed “IPAP” and the CPAP level, termed “EPAP.” The underlying principles of successful application of NIV are identical to those already described for pressure support and CPAP. In the nonintubated patient, CPAP takes on the added potential role of maintaining upper airway patency—also a useful characteristic in the postextubation period, in patients with laryngeal or glottic swelling, and in those at high risk for obstructive sleep apnea at that transitional time. As a rule, CPAP levels exceeding 10 cm H$_2$O are not well tolerated for extended periods. Because the majority of patients treated in the ICU breathe dry, oxygen-enriched gas with high levels of minute ventilation and are mouth breathers, adequate hydration of the gas stream is essential. This is particularly important to remember when the patient has been recently extubated, has impaired swallowing, and/or has a tendency to form and retain mouth and airway secretions.

**High-Flow Nasal Cannula**

For many patients who experience intolerable discomfort and need relatively little help in achieving effective ventilation, providing very high continuous flows of well-humidified gas through flexible, wide caliber nasal prongs (HFNC) may offer an appropriate alternative (Fig. 7-12). High gas flows provided in this way (30 to 60 L/min) are generally well tolerated and have both advantages and disadvantages compared to NIV (Table 7-6). With the oropharynx unencumbered, HFNC allows eating, normal oral hygiene measures, free communication, and expectoration. Some authors emphasize that the highly warmed and humidified inspired gas facilitates mucus mobilization as it avoids epithelial desiccation. Once in place, the cannulae are less likely than facial masks to be dislodged by position shifts and patient actions. HFNC interferes minimally with oral and upper airway inspection, bronchoscopy, and central venous cannulation and improves oxygenation during GI endoscopy.


**Table 7-6. Advantages and Disadvantages of HFNC**
The primary disadvantage of HFNC therapy in comparison to NIV is its limited ventilating potential and inability to generate anything more than minimal CPAP. HFNC cannot be easily continued during ambulation. Concerns regarding aspiration of upper airway secretions are not likely to be greater than with any noninvasive technique.

HFNC has been reported effective in a variety of settings that include mild ARDS, pneumonia, and cardiogenic pulmonary edema. In acute hypoxemic respiratory failure of modest severity, HFNC has been reported to fare somewhat better than both standard oxygen therapy and NIV in avoiding the need for intubation. During intubation, HFNC can help prevent hypoxemia. In the postoperative setting, HFNC may facilitate thoracoabdominal synchrony and increase end-expiratory lung volume. Immediately after extubation, HFNC may provide an effective bridge toward fully independent spontaneous breathing.

Mechanisms through which HFNC help improve ventilation continue to be investigated but appear to include washout of CO₂ from the upper airway, maintaining (or perhaps improving upon) spontaneous breathing efficiency, and maintenance of low level CPAP (<2 to 4 cm H₂O, flow rate dependent) that carries the potential to help counterbalance auto-PEEP as well as help prevent atelectasis and glottic obstruction (Table 7-7). Such high flows of lung-directed gas during expiration also gently retard exhalation, a feature superficially similar to the pursed lips breathing of patients with severe airflow obstruction that contributes to their dyspnea relief. A consistent observation made in patients receiving HFNC is that its application alters the breathing pattern by slowing breathing frequency and improves dyspnea. Whether this results entirely from improved ventilating efficiency or in part from dyspnea-attenuating upper airway reflex stimulation has not yet been clarified.

### Table 7-7. High-Flow Nasal Cannula (HFNC) Mechanisms of Action

1. Dead space washout of CO₂
2. Upper airway CPAP
3. Expiratory retard
4. Reflex
   - Attenuation of dyspnea
   - Alteration of breathing pattern
   - Reduces frequency-to-tidal volume ratio
Daily Assessment of the Ventilated Patient
The complex interactions of the patient and ventilator must be approached in a systematic fashion to optimize machine performance, establish synchrony, and minimize hazards (Table 7-8). A number of important questions must be asked in the daily assessment of the ventilated patient.

**Patient Status**

1. **Are cycling pressures excessive?**
   - Have they changed? Are pressures and tidal volumes consistent breath-to-breath? Are any changes attributable to alterations in resistance or compliance? Are breathing efforts synchronous with machine response?

2. **Are there reversible factors impeding airflow (bronchospasm, secretions) or worsening the compliance of the lung (new infiltrate, edema, atelectasis) or the chest wall (agitation, ascites, pleural effusion, abdominal distention)?**

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**Table 7-8. Bedside Evaluation of the Ventilated Patient**

<table>
<thead>
<tr>
<th>Mental status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous breathing rhythm</td>
</tr>
<tr>
<td>Minute ventilation requirement</td>
</tr>
<tr>
<td>Muscular strength</td>
</tr>
<tr>
<td>Secretion character and volume</td>
</tr>
<tr>
<td>Breathing effort and synchrony</td>
</tr>
<tr>
<td>pH and gas exchange</td>
</tr>
<tr>
<td>Breath sounds (intensity, distribution, symmetry)</td>
</tr>
<tr>
<td>Chest radiograph, chest CT, and echocardiogram</td>
</tr>
<tr>
<td>Mode of cycling</td>
</tr>
<tr>
<td>Cycling pressure (compliance/resistance)</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Complications and practical problems</td>
</tr>
</tbody>
</table>

Do secretion volume and character suggest respiratory infection, pulmonary hemorrhage, or ongoing aspiration of oropharyngeal or gastric contents? Is there any sign of unaddressed congestive heart failure, volume overload, volume depletion, or sepsis?

3. **What is the true minute ventilation requirement?**
   - To determine whether a high $[V \text{ with dot above}]_E$ is related to drive, metabolic requirement, acidosis, or iatrogenic hyperventilation, $[V \text{ with dot above}]_E$ must be interpreted in conjunction with PaCO$_2$, pH, and the physical examination. The diurnal range and variability of $[V \text{ with dot above}]_E$ is an important clue to the contribution of anxiety, agitation, or other reversible drivers of ventilation.

4. **How hard is the patient working to breathe?**
   - Is the patient making spontaneous breathing efforts? Are there signs of fatigue—elevated respiratory rate, abdominal paradox, irregular breathing rhythm? What are the pH and PaCO$_2$? During which mode of
ventilation, PEEP level, and position were blood gases assessed? The implications of respiratory acidosis, for example, are much different for CMV (underventilation), AMV (reduced drive), or low-level SIMV (reduced drive, inadequate strength).

5. **Is the patient still ventilator dependent?**

What is the ventilatory requirement and what is driving it (metabolic need, acidosis, agitation, hyperventilation)? Are cycling pressures high or low? Is the patient alert, and able to cough strongly? If the patient is unweanable, is dependency likely to change anytime soon? Should a tracheostomy be scheduled? Can NIV or HFNC be substituted?

6. **What is the patient’s comfort level?**

Is there evidence of agitation or distress? Does any discomfort relate to pain, visceral distention, anxiety, fever, or maladjusted ventilator? Is inadequate or excessive sedation being given?

7. **Is there evidence of patient-ventilator dyssynchrony?** Is it frequent or severe? How can triggering, flow, or cycle timing dyssynchrony be improved or eliminated?

8. **Should the patient be given a sedation holiday?**

9. **Can mobilization to chair be safely attempted?**

**Ventilator Status**

1. Are ventilator connections appropriate? Are the connectors tight? Is the ET tube cuff well sealed and is the circuit tubing kinked or water laden?

2. Is there a need to raise or lower the overall level of machine support for oxygenation or ventilation? Are plateau and driving pressures appropriate?

3. Are machine adjustments in mode, flow rate, corrected tidal volume, or PEEP required? Are airway pressures during ventilator cycles uniform and of expected shape, indicating synchrony of patient and ventilator breathing cycles?

**SUGGESTED READINGS**


Daoud EG, Farag HL, Chatburn RL. Airway pressure release ventilation: what do we know? *Respir Care.*


• Key Points

1. Impaired cardiac output is most likely to result from mechanical ventilation when intravascular volume is depleted, vascular reflexes are impaired, and the patient is inflated passively with high mean airway pressures.

2. All forms of alveolar rupture induced by mechanical ventilation—interstitial emphysema, pneumomediastinum, pneumoperitoneum, subcutaneous emphysema, cyst formation, pneumothorax, and systemic gas embolism—have been described in both infants and adults. Certain high-pressure ventilatory patterns inflict nonrupture damage, such as diffuse lung injury and bronchopulmonary damage (ventilator-induced lung injury).

3. The pathophysiology of tension pneumothorax involves cardiovascular as well as ventilatory compromise. Tension physiology can develop with only a minor portion of the lung collapsed if the lung is infiltrated, the airways are obstructed, or the lung adheres to the chest wall to cause loculations.

4. No single cause is responsible for all barotrauma. High peak airway cycling pressure, necrotizing pneumonia, heterogeneity of lung pathology, copious airway secretions, and duration of positive pressure ventilation are major predisposing factors.

5. The thoracostomy tube selected should be of such size and location to adequately drain the pleural air and/or liquid. The lung must be approximated to the parietal pleura whenever possible. Suction may be needed if an air leak is large, if it persists on water seal alone, or if fluid drainage is needed.

6. Failure to limit end-inspiratory plateau and driving pressures and to preserve a crucial minimum level of positive end-expiratory pressure during the early phase of acute respiratory distress syndrome may intensify preexisting alveolar damage. Later, in the disease process, when inflammation has degraded the collagen infrastructure of the lung, minimizing peak pressure helps prevent alveolar rupture, cyst formation, and pneumothorax.

7. Subacute and chronic complications of mechanical ventilation include fluid retention, redistribution of body water, infection, altered ventilatory drive, and respiratory muscle deconditioning.

8. Agitation during mechanical ventilation demands a systematic search through possible causes relating to the patient, the endotracheal tube and circuitry, and the ventilator itself.

ACUTE COMPLICATIONS OF MECHANICAL VENTILATION

Cardiovascular Impairment

Patients with good systolic function, normal sympathetic reflexes, and normal or increased intravascular volume tolerate mechanical ventilation well, especially if spontaneous triggering efforts continue. Blood return to the heart is driven across the venous resistance by the difference between the mean systemic vascular pressure upstream (MSP, largely determined by intravascular volume and venous tone) and intrathoracic vena cava pressure. Mean intrathoracic pressure rises during ventilation with positive pressure, especially when positive end-expiratory pressure (PEEP) is used or auto-PEEP is generated. This raised intrapleural pressure increases intracavitary right atrial pressure (but reduces the transmural pressure), causing cardiac output to fall unless MSP rises sufficiently to compensate (see Chapter 1). Major increases in lung volume may also compress the
vena cava and increase resistance in the region of the diaphragm. Initiating ventilatory support is most likely to compromise forward cardiac output in patients with depleted intravascular volume who fail to make breathing efforts. The effect may be quite different in patients with congestive failure in whom relief of the ventilatory burden, in combination with the reduction of left ventricular afterload that positive intrathoracic pressure provides, may dramatically improve forward output and reduce pulmonary vascular engorgement. (Conversely, resumption of a high ventilatory workload increases O$_2$ demands and lowers intrathoracic pressure sufficiently to seriously destabilize the ischemic or failing heart.) Impairment of cardiac output is particularly likely to occur in patients whose mean intrathoracic pressures rise highest (e.g., those with chest wall restriction, good lung compliance, and air trapping) and in patients who are volume depleted, β-blocked, or unable to venoconstrict adequately to boost MSP. Profound deterioration may occur in patients developing auto-PEEP immediately after the institution of positive pressure ventilation. Unlike hemorrhage and other states of volume depletion, compensatory heart rate responses to the lower output and blood pressure associated with positive pressure are often blunted. Usually, adverse reactions are most evident shortly after mechanical ventilation or PEEP is instituted, as slowly adapting compensatory changes in intravascular volume and vessel tone may attenuate these effects over time.

**Barotrauma**

**Pathogenesis of Alveolar Rupture**

The varied forms of pulmonary barotrauma—interstitial emphysema, pneumomediastinum, pneumoperitoneum, subcutaneous emphysema, cyst formation, and pneumothorax (PTX)—are troublesome iatrogenic consequences of intensive care. Although PTX may arise from such diverse medical problems as pulmonary infection or infarction, *Pneumocystis* pneumonia, or spontaneous or cough-induced rupture of a pleural bleb, a confined set of etiologies accounts for most PTX in the intensive care unit (ICU): pulmonary and pleural punctures, lung necrosis, and ventilator barotrauma. Projectiles, sharp instruments, and displaced rib fractures cause PTX by direct puncture of the visceral pleura. PTX may also complicate any medical procedure in which a needle enters the thorax, especially thoracentesis, pleural biopsy, transthoracic aspiration of a pulmonary mass, and central line placement. (Therefore, if a subclavian or internal jugular central line must be placed, it is prudent to select the side with an existing chest tube.) If air enters the pleural cavity inadvertently via a needle without inflicting lung injury, the gas will spontaneously reabsorb, often without the need for intervention. Discrete single punctures of the lung are less likely to cause problems than multiple punctures or slashing actions of the bevel of the needle. Disruption of the visceral pleura and necrotizing pulmonary infections may also cause PTX.

With increased awareness of the dangers of high airway pressure, ventilation-associated barotrauma now occurs much less frequently than in previous decades. Direct rupture of the visceral pleura undoubtedly occurs as a consequence of regional overdistention by positive pressure in many patients with diseased or injured lungs, but the barotrauma that complicates mechanical ventilation can also develop by a more circuitous path. Rupture of weakened alveolar tissues is particularly likely to affect “nonpartitional” or “marginal” alveoli, which have bases contiguous to relatively immobile structures—vessels, bronchioles, or fibrous septae. During positive pressure ventilation (or severe blunt chest injury that occurs with the glottis closed), alveolar pressures rise more than interstitial pressures, allowing pressure gradients to develop between marginal alveoli and the contiguous perivascular connective tissues. If rupture occurs, extra-alveolar gas follows a pressure gradient down the path of least resistance, tracking along the perivascular sheaths toward the hilum. The interstitial emphysema produced en route may be detected against the radiopaque background of infiltrated lung as lucent streaks and small cysts that do not correspond to the bronchial anatomy. The gas continues to track centrally, forming a pneumomediastinum that may or may not be evident on routine films (see Chapter 11).
In the absence of preexisting mediastinal pathology, extra-alveolar gas dissects along fascial planes, usually decompressing into the soft tissues of the neck (subcutaneous emphysema) or retroperitoneum (pneumoperitoneum). PTX occurs in a significant minority of such cases (perhaps 20% to 30%) when soft tissue gas ruptures into the pleural space via an interrupted or a weakened mediastinal pleural membrane. Interstitial emphysema, pneumomediastinum, and subcutaneous emphysema have little hemodynamic significance and seldom affect gas exchange significantly in adults. Because their presence signals alveolar rupture and the potential for PTX to occur, these signs are important to detect in the ventilated patient. Pressure gradients usually favor decompression of interstitial gas into the mediastinum. However, when normal bronchovascular channels are blocked, gas accumulates locally or migrates distally to produce subpleural air cysts that compress parenchymal vessels, create dead space, increase the ventilatory requirement, and cause major problems for ventilation-perfusion matching. The development of cystic barotrauma is an ominous finding that usually presages tension PTX a short time afterward.

**Bronchopulmonary Injury**

Until quite recently, the development of bronchial damage was believed to occur only rarely in adult patients. Autopsy studies of patients ventilated at moderately high pressures for extended periods, however, have demonstrated that small airways unsupported by cartilage can sustain considerable damage at high airway pressures. Airway distortion predisposes to cystic parenchymal damage, disordered gas exchange, and impaired secretion clearance.

**Cystic Barotrauma**

Widespread cystic barotrauma is most likely to develop in young patients with necrotizing pneumonitis, narrowed airways, and retained secretions. Alveolar rupture and focal gas trapping are keys to its pathogenesis. As predicted by the law of Laplace ($P = \frac{2T}{R}$), the pressure ($P$) required to maintain a fixed tension ($T$) in the wall of a spherical structure falls as its radius ($R$) increases. Therefore, it is not uncommon for a cyst created by positive airway pressure to grow quickly to a large dimension (>10 cm in diameter). Once underway, cystic barotrauma tends to be pernicious and self-reinforcing. As cysts develop, they compress normal lung tissue, stiffening the lung and increasing the airway pressure needed for effective ventilation. Furthermore, blood flow diverts away from areas of cyst expansion, creating dead space that increases the ventilatory requirement and therefore the mean alveolar pressure. Increased peak and mean airway pressures accentuate the tendency for further lung damage, whereas higher requirements for alveolar ventilation tend to keep the patient dependent on the ventilator. Secretion management, treatment of infection, and most importantly, reduction of airway pressure are fundamental to effective management.

**Systemic Gas Embolism**

For patients with acute respiratory distress syndrome (ARDS) ventilated with high tidal pressures and maintained with relatively low left ventricular filling pressures (pulmonary arterial “wedge pressures”), peak and mean alveolar pressures may exceed pulmonary venous pressures in certain lung regions. If alveolar rupture opens and maintains a communication pathway to the vascular system, this pressure gradient may drive gas into systemic circulation. Although rare, microbubbles can then cause vasospasm, seizure, stroke, or myocardial infarction (MI). Usually, the MI is inferior, as the buoyant air percolates into the right coronary artery, which lies anteriorly and superiorly in the supine position.

**Uncomplicated Pneumothorax**

Ordinarily, the visceral and parietal pleural surfaces are approximated during both phases of the respiratory cycle. The negative pressure between them is developed by the joint tendencies of the chest wall to expand and
the lungs to recoil to their natural resting volumes. At equilibrium, these opposing forces create a moderately negative pleural pressure. PTX disrupts the normal relationship of the lung to the chest wall. The lung collapses toward its resting volume. Simultaneously, PTX allows the chest wall to expand toward its unstressed volume, which occurs at approximately 60% of the normal vital capacity. The natural tendency of the chest wall to expand—"the counterspringing effect"—is diminished or lost when thoracic volume increases. The gas that separates them impairs coupling between the lung and chest wall. Outward migration of the chest wall puts the diaphragmatic "bellows" at a mechanical disadvantage. Expansion of the chest wall also shortens the resting length of the inspiratory muscles, placing them on a less advantageous portion of their length-tension relationship. Less obviously, the total force developed by the muscles of the chest wall normally distributes over a larger surface area than that offered by the collapsed lung. Therefore, even if the inspiratory muscles generate the same intrapleural pressure, the total force applied to the lung is reduced in proportion to the degree of lung collapse. As tidal excursions of the unaffected lung increase to maintain ventilation, elastic and flow-resistive work increased. This increase is well tolerated by healthy patients with adequate ventilatory reserve. However, those with significant airflow obstruction, neuromuscular weakness, or parenchymal restriction may experience dyspnea, progressive hypoventilation, and respiratory acidosis.

**Tension Pneumothorax**

The term tension PTX implies sustained positivity of pleural pressure. The intrapleural pressure exceeds atmospheric pressure during expiration and for a portion of neural inspiration, as well. A tension component can develop when a ball valve mechanism pumps air into the pleural cavity during spontaneous breathing but occurs much more commonly during positive pressure ventilation. Positive intrapleural pressure expands the ipsilateral chest cage, rendering the muscles less-efficient generators of inspiratory pleural pressure. A shifting mediastinum helps the affected side to accommodate to the increasing pressure but encroaches on and deforms the contralateral hemithorax, compromising lung expansion. Eventually, rising pleural and central venous pressures impede venous return sufficiently to cause hemodynamic deterioration. It should be emphasized that tension can develop without lung collapse or even major volume loss (e.g., when the lung is heavily infiltrated, air trapped, or regionally bound by pleural adhesions). Vigorous inspiratory efforts tend to maintain intrapleural pressure (averaged for both lungs over the entire respiratory cycle) nearly at normal levels until the patient fatigues, is sedated, or receives increased machine assistance. Then, abrupt hemodynamic deterioration may occur as mean pleural pressure rises sharply. Such considerations explain why many patients who develop pneumothoraces while mechanically ventilated show a tension component and why ventilated patients with PTX who receive sedating or paralyzing drugs frequently undergo abrupt hemodynamic deterioration. For the nonintubated patient, muscle fatigue and respiratory arrest may precede the cardiovascular collapse described classically with the tension PTX syndrome.

**Risk Factors for Barotrauma**

Although the peak airway cycling pressure has been cited frequently as the most important risk factor for ventilator-related barotrauma, it clearly is not the only one (Table 8-1). In fact, magnitude of tidal pressure may be overwhelmed by other cofactors. The correlation between airway pressure, driving pressure, and PEEP to barotrauma is not a tight one. A necrotizing parenchymal process, inhomogeneous lung pathology, young age, excessive airway secretions, and duration of positive pressure ventilation are major predispositions. The process of alveolar rupture is one that seems to require sustained hyperexpansion of fragile alveoli. Therefore, the mean alveolar pressure, averaged over an entire respiratory cycle, may be an important (but not sole) cause. As major determinants of peak and mean alveolar pressures, minute ventilation requirement and high levels of PEEP contribute to the PTX hazard. (PEEP itself without high inflation pressure contributes little to the risk of
barotrauma, especially if applied within the range over which lung recruitment is its primary action.) Peak dynamic \( (P_D) \) and peak static \( (P_S) \) or “plateau”) airway pressures seem to contribute most to the multivariate risk equation. Peak dynamic airway pressure can be reduced by improving lung compliance, reducing tidal volume \( (V_T) \), driving pressure or PEEP, lowering airflow resistance, or slowing peak inspiratory flow rate. On first consideration, it might seem that \( P_S \) (the pressure that acts in conjunction with thoracic compliance to determine overall lung volume and alveolar stretch) should correlate even more closely with PTX than \( P_D \). However, although \( P_S \) does bear a strong relationship to PTX, airway resistance varies greatly among the bronchial channels of a nonhomogeneously affected lung, so that increasing the dynamic pressure within the central airway may encourage regional overdistention and alveolar rupture in channels with open pathways to weakened alveoli. Ball valving may also occur. Therefore, raising the peak flow rate is not risk free. On the other hand, slowing the rate of inspiratory flow prolongs alveolar distention, increasing the mean alveolar pressure. This is true especially for patients with severe airflow obstruction. Improving airway resistance or lung compliance and reducing alveolar pressure by lowering \( V_T \) and/or PEEP are preferable methods for lowering \( P_D \).

There does not seem to be a sharp threshold value of peak ventilator cycling pressure below which lung rupture fails to occur. As a rule, however, PTX becomes much more likely at peak ventilator cycling pressures greater than 40 cm H\(_2\)O. A peak tidal pressure greater than 35 cm H\(_2\)O usually achieves or exceeds the alveolar volume corresponding to total lung capacity in a patient with a normal chest wall. Conversely, when the chest wall is stiff, high plateau pressures may be well tolerated. Secretion accumulation, blood clots, or foreign objects can increase the degree of nonhomogeneity or create ball-valve phenomena that increase barotrauma hazard. The crucial roles of mechanical and structural nonhomogeneity may explain why PTX tends to develop 1 to 3 weeks after diffuse lung injury, a time when some regions are healing while others remain actively inflamed.

### Table 8-1. Predispositions to Barotrauma

<table>
<thead>
<tr>
<th>PATIENT FACTORS</th>
<th>MACHINE ADJUSTMENTS</th>
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<tbody>
<tr>
<td>Necrotizing lung pathology</td>
<td>High peak cycling pressure</td>
</tr>
<tr>
<td>Secretion retention</td>
<td>High mean alveolar pressure</td>
</tr>
<tr>
<td>Nonhomogeneous parenchymal disease</td>
<td>High driving pressure</td>
</tr>
<tr>
<td>Duration of ventilation</td>
<td>High minute ventilation</td>
</tr>
</tbody>
</table>

Diagnosis of Barotrauma

**Clinical Features of Pneumothorax**

Early recognition of PTX is of paramount importance for patients ventilated with positive pressure because of their proclivity to develop tension. During episodes of acute clinical deterioration compatible with PTX, the mortality risk rises when physicians delay intervention, awaiting roentgenographic confirmation. Pleuritic chest
pain, dyspnea, and anxiety comprise the most common symptoms of uncomplicated PTX. Symptoms indicative of other forms of extra-alveolar air that may precede PTX include transient precordial chest discomfort, neck pain, dysphagia, and abdominal pain. These nonspecific symptoms often are transient. Tension PTX frequently provokes tachypnea, respiratory distress, tachycardia, diaphoresis, cyanosis, or agitation. For patients receiving volume-cycled ventilation, the airway manometer usually (but not always) shows increased peak inspiratory (and peak static or plateau) airway pressures as PTX develops, especially if tension is present. Compliance of the respiratory system usually falls from previous values. During volume cycling, the ventilator may “pressure limit” or “pop off,” resulting in ineffective ventilation. During pressure-controlled ventilation, a decreased tidal volume and/or minute ventilation may be the only clue to increasing ventilatory impedance.

Close examination of the affected hemithorax often reveals signs of hyperexpansion with unilateral hyperresonance, tracheal deviation, diminished ventilatory excursion, and reduced breath sounds on the affected side. The examination must be performed carefully, as massive atelectasis can present a similar clinical picture, simulating PTX on the contralateral side. Auscultation and percussion are essential. Massive gas trapping with auto-PEEP is another effective mimic of PTX, especially if hyperinflation or infiltration is distributed asymmetrically. Palpation of the cervical tissues and suprasternal notch is important to detect subcutaneous emphysema or a trachea deviated away from the side of tension. Tension is reflected in elevations of central venous, right atrial, and pulmonary arterial pressures. Such hemodynamic changes generally do not occur during atelectasis.

**Radiographic Signs of Barotrauma**

**Extra-alveolar Gas**

Extra-alveolar air in the lung parenchyma can manifest as interstitial emphysema or as subpleural air cysts. Both are easiest to detect when the parenchyma is densely infiltrated. Sharp black lines that outline the heart, great vessels, trachea, inferior pulmonary ligament, or diaphragm suggest mediastinal emphysema, even when the pleural membrane itself cannot be visualized (Fig. 8-1). The “complete diaphragm” sign indicates that the heart is separated from the diaphragm by a cushion of air.

Subcutaneous emphysema, subdiaphragmatic air, and pneumoperitoneum are other manifestations of barotrauma that may precede or coexist with PTX. Subpleural air cysts commonly are often seen in basilar regions.
FIGURE 8-1. Radiographic signs of barotrauma: (1) visible visceral pleural line, (2) deep sulcus sign, (3) radiolucency localized to the upper abdomen, (4) inverted hemidiaphragm, (5) air-fluid level, (6) mediastinal shift, (7) subpleural air cyst, (8) interstitial emphysema, (9) complete diaphragm sign, and (10) pneumomediastinum.

Pneumothorax
Although bedside ultrasound may quickly raise suspicion of PTX, certain radiographic signs deserve emphasis for its confirmation. A smooth, two-sided visceral pleural line is diagnostic but must be distinguished from a skin fold and other artifacts at the body surface. The magnification feature is often needed if the lung is otherwise normal, especially when digitized films are viewed from a remote monitor. (By providing an air-tissue contrast, infiltrates make the job of PTX detection much easier.) Even when pulmonary infiltrates are extensive, a pleural line may be particularly difficult to detect on a standard supine view if pleural air loculates anteriorly or if ribs or mediastinal vessels obscure the pleural margin. Two useful markers of occult PTX visible on supine films are the “deep sulcus” sign and hyperlucency centered over the ipsilateral abdominal upper quadrant. For bedridden patients, a lateral decubitus view allows air to collect along the upper margin of the hemithorax, facilitating visualization. An expiratory chest radiograph also may prove revealing. (Although the volume of intrapleural air remains constant, it occupies a greater percentage of the available ipsilateral thoracic volume.) PTX under tension can be suspected strongly from a single film when diaphragmatic inversion or extreme mediastinal shift occurs. A sequence of films demonstrating progressive migration of the mediastinal contents into the
contralateral hemithorax indicates that the diagnosis was delayed but confirms its validity. Life-threatening tension PTX can exist without complete lung collapse or mediastinal displacement if a portion of the lung adheres to the pleura, if the lung is densely infiltrated, if the airway is obstructed, or if the mediastinum is immobilized by infection, fibrosis, neoplasm, or previous surgery. A preexisting chest tube may not prevent tension from developing if the tube is clogged, nonfunctional, or inadequate to evacuate a large air leak; if the pocket drained is loculated; if the drainage holes are within the major fissure; or if intraparenchymal tension cysts coexist. In fact, by indicating the presence of and tendency for tissue rupture, the presence of a chest tube should not negate suspicion for an inapparent PTX on the same side.

**Value of the Computed Tomography Scan**

The thoracic computed tomography (CT) scan is an invaluable aid in determining whether lucency represents parenchymal or pleural air. In fact, accurate placement of a chest tube into a loculated pocket of gas or fluid may require insertion under direct CT guidance. When doubt exists regarding the effectiveness of the chest tube in draining gas or fluid and/or the exact placement of the tube, CT performed with the tube connected to an appropriate level of suction is currently the “gold standard.” Assuming that the patient can be transported safely, modern CT scanning equipment can acquire a volumetric (helical or spiral) data set very quickly (within seconds). Reconstruction of a two-dimensional image can then be initiated along sagittal and coronal as well as the traditional axial plane. Indeed, highly informative three-dimensional reconstruction is now being applied with increasing frequency, imaging that usually leaves little doubt regarding the relevant anatomy and may even reveal a site of visceral rupture.

**Management of Pneumothorax and Pleural Effusion**

**General Principles**

Pulmonary barotrauma developing in the setting of acute lung injury is a self-perpetuating, autoamplifying, and potentially lethal process that must be prevented. After extra-alveolar air begins to manifest in its cystic form, impaired gas exchange often forces an increase in minute ventilation requirement and, therefore, in mean airway pressure. In turn, higher mean airway pressure may worsen the tendency for alveolar rupture. Key principles for avoiding barotrauma (Table 8-2) include (1) treat the underlying disease, especially suppurative processes; (2) maintain excellent bronchial hygiene but minimize unnecessary coughing; (3) reduce the minute ventilation requirement by limiting agitation, fever, metabolic acidosis, and bronchospasm; and (4) reduce peak and mean airway pressures by limiting PEEP and tidal volume, by permitting hypercapnia, and by increasing the percentage of spontaneous versus machine-aided breaths. During volume-cycled ventilation, reducing tidal volume modestly (e.g., by 100 to 300 mL) may greatly reduce $P_D$ and $P_S$. Peak flow should be set to the lowest value that satisfies inspiratory demand without incurring additional patient work or auto-PEEP, thus lowering peak dynamic (but not peak static or mean alveolar) pressure. Although several modes of ventilation have been advocated to reduce peak airway pressure (high-frequency, pressure-supported, and pressure-controlled ventilation), their therapeutic efficacy in preventing barotrauma is unproven.

**Table 8-2. Preventing Ventilator-Related Lung Rupture**

<table>
<thead>
<tr>
<th>Minimize minute ventilation</th>
<th>Limit peak and plateau inflation pressures</th>
</tr>
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<tbody>
<tr>
<td>Use lower $V_T$ and driving pressure</td>
<td>Decrease I:E ratio</td>
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</table>

P.170
Decrease bronchial obstruction
Improve lung compliance
Encourage gentle spontaneous breathing

**Chest Tube Drainage**

**Indications for Thoracostomy**

Vigilant observation and conservative management are appropriate options in the spontaneously breathing, uncompromised patient with a very small PTX. If the patient is breathing spontaneously, simple observation with close radiographic follow-up is a reasonable strategy only for such well-compensated patients who remain alert and comfortable without symptoms after thoracentesis, aspiration needle biopsy, or central line placement. Many such patients will not require more aggressive management. (The same is not often true for patients receiving positive pressure ventilation, especially if ventilating pressures are high.) However, follow-up radiographs (or CTs) must demonstrate stability improvement. The best course is usually to place a small and generally well-tolerated “pig tail” catheter.

Although spontaneous resolution of PTX is a slow process, an air collection that fails to show convincing improvement over several days may indicate an ongoing leak, with equilibration between the rates of leakage and absorption. After leakage stops, the absorption of intrapleural air occurs at a variable rate, averaging approximately \[(\text{original }\%)/(1.5\%)\] each day. Even a moderate PTX may take more than a week to resolve. (For example, a 15% PTX would be expected to reabsorb completely in 15/1.5 = 10 days.) During this period, the partially collapsed lung may clear secretions poorly. Because large collections of undrained pleural air predispose to infection of the lung or pleural space, hypoxemia, and proteinaceous pleural fluid collections, they must be evacuated by catheter aspiration or chest tube. The high risk of tension mandates early decompression in the mechanically ventilated patient. Other patients to consider for early intervention are those with ipsilateral pneumonia or secretion retention, ventilatory insufficiency, or high ventilation requirements.

**TUBE OPTIONS**

The ideal chest tube system provides a reliable, low impedance conduit that ensures efficient, unidirectional evacuation of gas and liquid from the chest. It should produce subatmospheric intrapleural pressure and reapproximate the lung to the chest wall. To be in best position for drainage of unloculated air, the tube should be directed superiorly and anteriorly. Small "pig tail" catheters and small caliber chest tubes can be introduced anteriorly in the second intercostal space, but for reasons of relative comfort or cosmetics, are often placed laterally. Tubes to be placed in loculated pockets are best inserted by an interventional radiologist. Large tubes are best introduced laterally in the midaxillary line of the sixth-to-seventh interspace and are directed upward, taking care to avoid entry into a fissure. Starting from a lower interspace, the operator should be careful to avoid subdiaphragmatic placement. When the PTX is distributed evenly (unloculated) and suction is used, the actual position of the tube tip makes little difference. However, if loculations develop, a poorly placed chest tube, especially one not connected to suction, may fail to evacuate the appropriate region.

Although large tubes usually are needed to drain substantial collections of fluid or massive ongoing air leaks, chest tubes placed for simple air drainage are usually 28 French in caliber or smaller. Iatrogenic pneumothoraces without major air leak often can be managed in stable patients with short flexible tubes of very small diameter (usually pigtail catheters). These can be attached to a drainage system (with or without suction) or to a lightweight, one-way flutter valve (Heimlich valve) to facilitate ambulation (Fig. 8-2). Larger tubes are selected if substantial liquid drainage is also needed. Tube radius is a major determinant of the evacuation capability of the system.
DRAINAGE APPARATUS

One-way drainage of air usually is ensured by a water seal as part of a classical “three-bottle” system. In recent years, lightweight, self-contained, integrated function, disposable plastic units are used almost exclusively (Fig. 8-3). A collection chamber (or “bottle,” a label used in deference to the original equipment serving the same function) is inserted in tandem and proximal to the water seal column. The water seal chamber is separated from the collection chamber because accumulated liquid drainage would make air leakage difficult to visualize and, more importantly, would create sufficient back pressure to hinder lung expansion as fluid accumulates. Regulation of the suction pressure applied to the chest tube, a function once done by a water-filled and continuously bubbling “suction regulating” chamber, is now accomplished by a simple noise-free mechanical or needle valve (Fig. 8-3).

FIGURE 8-2. One-way flap or flutter valve. The flutter (Heimlich) valve opens only when sufficient positive pressure builds within the chest tube. Such devices are intended primarily for low-volume pleural air leaks without substantial fluid drainage. They enhance mobility for ambulatory patients.

**MONITORING TUBE FUNCTION**

Fluid movements in the water seal tube reflect tidal variations of intrapleural pressure adjacent to the tube. Without suction applied, fluctuations of liquid within a dependent loop of drainage tubing or of the water seal (“tidaling”) can provide useful clinical information. (Tidal fluctuations are much smaller during suction.) An abrupt increase in tidal magnitude suggests undrained air surrounding the tube, lobar atelectasis, upper airway obstruction, impaired secretion clearance, or hyperpnea. Decreased tidal magnitude can reflect resolution of any of these problems, partial obstruction of drainage, or decreased air leakage through a bronchopleural fistula (BPF). Absent fluctuations may be explained by tube obstruction with fibrin, blood clots, or extrinsic compression. Because of the risks of infection, the chest tube should be removed as soon as it no longer fulfills a useful function. Because 25 to 100 mL of liquid will form each day within the normal pleural space, drainage of this amount is expected through a functioning tube that has full access to the pleural space. (Tubes draining
loculated spaces may be patent despite lesser output.) If the tube is patent, noticeable fluctuations within the water seal chamber should occur during moderate respiratory efforts.

A “dead tube” (<50 mL/24 hours of drainage, no gas leak, and no respiratory fluctuation) should either be made functional or pulled. A tube that drains empyema, blood, or thick fluid can often be maintained patent by periodic “stripping.” Quite often, a clogged or ineffective tube can be reopened at least transiently by sterile injection of an intrapleural fibrinolytic (e.g., alteplase or tissue plasminogen activator [TPA]), followed by a brief period of clamping. When a complicated effusion (without ongoing air leak) requires drainage, injecting 25 to 50 mg of 100 mL alteplase in approximately 100 mL of saline into the pleural pocket and letting it act behind a chest tube clamped for several hours may break up loculations and reestablish effective drainage. This process may need repeating multiple times over several days. Although experience has shown that intrapleural bleeding and/or alteration of the systemic coagulation profile rarely occur, TPA instillation is not entirely without risk. A tube that clogs repeatedly presents a genuine risk of infection and probably requires extraction (“pulling”) and/or replacement. Another tube or more aggressive surgical approach, such as video-assisted thoracoscopic debridement, should then be considered if the need for draining additional drainage is still apparent. If the water seal level rises (toward the patient) and ceases to fluctuate with respiration after several days of declining drainage, pleural reapposition probably has occurred, and the tube should be removed after radiographic confirmation. The rising level reflects sealing of the air leak and subsequent absorption of the air contained within the chest tube.

Persistent bubbling at the water seal signals an air leak within the lung, tubing, or connections. If the leak is within the lung, its magnitude can be quantified during volume-cycled mechanical ventilation by comparing the set inspiratory volume delivered by the machine to the recovered exhaled tidal volume. If the set (machine delivered) and expired tidal volumes are nearly equivalent, air leakage is likely to originate external to the lung. Cessation of the air leak when the tube is clamped near the chest wall indicates a BPF or air entry at the incision site. The latter can be excluded by careful approximation of the skin edges and the application of airtight occlusive dressings. If the leak does not stop after clamping near the chest wall, there has been a breach of drainage system integrity. Migratory (transient) clamping of the tubing (moving away from the patient) will then allow more precise localization. Each connection should be carefully inspected.

Suction

INDICATIONS FOR SUCTION

Natural pressure gradients (fluid siphon effects, expiratory contractions, inspiratory development of positive pressure during mechanical ventilation) are often adequate to empty the pleural space of gas and liquid. However, suction will generally be needed for large air leaks or for drainage of viscous effusions or blood. When the lung is entirely surrounded by gas, pressure applied to one portion of the pleural surface distributes equally throughout the hemithorax. However, when normal pleural surfaces are approximated, the negative pressure applied to one area transmits poorly to other regions. The explanation is that lung tissues adjacent to the tube effectively isolate the pocket of negative pressure. In addition, the tissues may be drawn into the “eyes” of the tube, preventing general transmission of applied negative pressure. When this happens, increasing suction only increases the risk for local tissue injury. For similar reasons, tubes placed inadvertently into a major or minor fissure are surrounded by very pliable lung surfaces and tend to drain poorly—but this is not invariably true. Adhesions with loculation also may impede pressure transmission—negative or positive. Massive amounts of fluid or air can collect, and tension can develop in sectors remote from a functioning but isolated tube. In this instance, multiple tubes in different locations may be required. Unless the draining fluid is unusually viscid, suction usually can be discontinued (but the water seal maintained) when gas bubbling stops.
SUCTION SYSTEMS

Two types of suction system are used to regulate safe levels of suction pressure. The Emerson suction generator, previously used for decades but now employed with diminishing frequency, links a servomechanism to a fan. A high-capacity, low impedance, and time-tested system is capable of maintaining essentially constant negative pressure at flow rates up to 40 L/min. If power is interrupted, air escaping from a BPF can vent between the fan blades, preventing tension. If increased gas leakage develops in the system, the servomechanism increases the evacuation rate to maintain constant pressure. It is important to recognize, however, that with older units the pressure is sensed within the apparatus itself, and the manometer will continue to register a substantial level of negative pressure, even if the pump becomes completely disconnected from the patient. If set up as recommended by the manufacturer, the collection and water seal functions are combined. This efficiently protects the motor against damage but causes problems when there is substantial liquid drainage. If suction must be maintained during transport, special battery-operated pumps should be used.

Several commercially available units incorporate a pressure-regulated three-bottle (three-chamber) system in a single molded plastic container (Fig. 8-3). A needle valve or a third chamber added in series to fluid collection and water seal columns serves as a pressure governor, modulating excessive wall suction pressures (-80 to -200 cm H\textsubscript{2}O) to the desired level (typically <30 cm H\textsubscript{2}O). For unvalved systems of this type, the filling level of the vacuum control column determines and limits the degree of applied suction. Suction is increased until continuous gentle bubbling occurs in the control chamber,

indicating that sufficient negative pressure has been applied to the water surface to offset the hydrostatic column. Continuous gentle bubbling in the control chamber must be maintained throughout both phases of the respiratory cycle to ensure the desired level of suction. Increasing the applied vacuum then only serves to increase fluid perturbations in the suction control bottle, leaving the suction applied to the pleural space unaffected. (The magnitude of bronchopleural air leakage must be gauged from the water seal column.) As opposed to needle valve controllers, these three-bottle units are inherently noisy and are slowly disappearing from the clinical scene. When using traditional equipment, three easily remediable problems commonly cause failure to deliver the desired level of negative pressure: fluid accumulation in the water seal chamber (common with Emerson pump), evaporation from the pressure-limiting tube of a three-bottle system, and the development of a large, fluid-filled dependent loop. Of these, only the latter remains a concern with integrated disposable plastic systems now in widespread use.

**Pulling the Tube**

Provided that gas leakage ceases and any pleural liquid collection has been effectively drained, the tube can be removed safely 24 to 48 hours after suction has been discontinued, provided that no air leakage occurs during coughing and a PTX is not visible radiographically. For patients who have experienced PTX, it is wise to clamp the chest tube for 2 to 4 hours prior to the “preextraction” X-ray, as very slow leaks may elude brief bedside inspections of the water seal apparatus. Tubes placed to drain pleural effusion without PTX can be extracted when no longer functional (see earlier). Even when no gas leak is present and no air collection is suspected, however, some physicians defer extraction of a functional chest tube until the mechanically ventilated patient is extubated. This precaution is controversial, however, and the uncomfortable presence of an unnecessary chest tube may require sedation or analgesia that could delay weaning.

**Special Problems of Barotrauma**

**Extensive Subcutaneous Emphysema**

A small amount of subcutaneous emphysema very frequently is palpable around the chest tube entrance site.
However, extensive unilateral emphysema suggests focal accumulation of air under pressure near the thoracostomy wound. Forced exhalation, straining, and coughing tend to drive pleural gas into soft tissues. Extensive subcutaneous emphysema often indicates inadequate evacuation of a large air leak and should prompt careful examination for problems that might decrease system efficiency. In the absence of these, management options include increasing suction pressure, changing to an evacuation system with greater capability, readjusting tube position, or placing a second chest tube to diminish the impedance to pleural emptying. Another potential cause is migration of the most proximal drainage hole from the pleural space and into the soft tissues.

**Persistent Bronchopleural Fistula**

Nonresolving air leaks occur commonly after rupture of emphysematous blebs, after subtotal pulmonary resection, and during ventilator treatment of ARDS. In the latter setting, the development of a large BPF portends a poor prognosis for survival, largely because BPF is a marker of underlying disease severity—or imprudent ventilator management. Adequate gas exchange usually can be maintained by conventional ventilator adjustments or by one of the following outlined techniques. Interestingly, the effluent from BPF contains considerable CO$_2$, especially if the lung parenchyma is relatively healthy. Although the “flow-through” ventilation provided by the fistula is less efficient than tidal breathing, the gas that exits the fistula has participated in gas exchange and is not entirely “wasted.” For this reason, effective tidal volume is greater than that measured though the exhalation line of the ventilator circuit.

**Routine Management of a Bronchopleural Fistula**

To manage a BPF, the underlying pathology must be reversed, the airway secretions must be cleared, $[V \text{ with dot above}]_E$ must be minimized, and good nutrition must be ensured (Table 8-3). A large body of clinical data suggest that approximating the visceral and parietal pleura facilitates healing of pleural rents. The initial approach to management may include tube repositioning (preferably with CT guidance), insertion of a second tube, and/or a trial of increased suction in an attempt to oppose the pleural surfaces more tightly. However, when the leak remains unsealed, increased suction may simply intensify or perpetuate flow through the fistula. If increasing suction fails, lowering or removing the suction may, in rare instances, promote healing by relieving tension on the margins of the tear. Increased lung collapse may compromise gas exchange, however. In refractory cases, thoracoscopic closure may be needed (see following).

<table>
<thead>
<tr>
<th>Table 8-3. Techniques for Managing Bronchopleural Fistula</th>
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<tr>
<td><strong>GENERAL MEASURES</strong></td>
</tr>
<tr>
<td>Reverse underlying pathology</td>
</tr>
<tr>
<td>Clear retained airway secretions</td>
</tr>
<tr>
<td>Minimize $[V \text{ with dot above}]_E$ and pressure requirements</td>
</tr>
<tr>
<td>Improve nutritional status</td>
</tr>
<tr>
<td>Change body position</td>
</tr>
<tr>
<td>Reposition chest tubes</td>
</tr>
<tr>
<td>Increase suction force if PTX persists on radiographs or CT</td>
</tr>
<tr>
<td>Trial of decreased suction if high suction is ineffective</td>
</tr>
<tr>
<td><strong>SPECIALIZED MEASURES</strong></td>
</tr>
<tr>
<td>High-frequency ventilation</td>
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Management of a life-threatening air leak in the mechanically ventilated patient can prove very difficult. Several techniques have been described for modifying the apparatus, either to prevent flow through the chest tube during inspiration or to maintain a common level of PEEP in the airway and the affected pleural space. None of these has gained widespread support. In some instances, independent lung ventilation has been tried successfully, but this intervention requires heroic supportive efforts. A few studies conducted primarily in children suggest that high-frequency ventilation (HFV) is associated with a lower incidence of barotrauma. Moreover, some reports indicate that HFV by oscillation can help to close large air leaks by reducing the flow through the low-impedance, high-compliance (leaking) pathway, but this remains an inconsistent and as yet unproven possibility. Surgical intervention must be considered, especially for less critically ill patients with cystic or bullous lung disease. Although long periods (occasionally weeks) of observation and manipulation of the drainage system have traditionally preceded operation, a more aggressive approach is now frequently used because of improved and somewhat less-invasive techniques. Primary suturing or stapling of the injured area often complemented by talc poudrage or pleural abrasion usually suffice. Closure by video-assisted thoracoscopic surgery (VATS) can be attempted in suitably stable, nonhypoxemic patients who can be adequately ventilated during the procedure. In the case of large fistulas, direct tamponade by a pedicle flap, lobectomy, or tissue resection may be needed. Chemical pleurodesis with talc, doxycycline, or tetracycline (where available) has occasionally been used as an alternative to surgical intervention, but this treatment must be considered hazardous and of uncertain merit, especially if the leak is large. Attempts at chemical sclerosis are seldom successful unless performed with meticulous technique. Chemical closure is unlikely to be achieved in the presence of multiple adhesions, large air leaks, or inability to oppose the pleural surfaces.

Occasionally, successful, transbronchoscopic techniques that occlude the airway with autologous clot, tissue glue, or a mixture of thrombin and fresh frozen plasma may close a persistent BPF and obviate the need for surgery. Pleural instillation of sterile talc (by insufflation or as a slurry), tetracycline, or autologous blood (a blood patch) using a chest tube may seal a very small but persistent leak, but such pleurodesis attempts are generally poorly advised, hazardous, and may complicate a later surgical approach. None can be accomplished safely in the unstable patient, and because such procedures require at least transient clamping of the chest tube, tension physiology may ensue. Intervventional bronchoscopy to insert one or more way valves (as is recently done for volume reduction in emphysematous patients) has conceivable merit for a “slow leaker” in an inoperable patient, but there is no published information regarding this highly experimental and unvalidated technique.

Ventilator-Induced Pulmonary Edema, Lung Injury, and Volutrauma

Pathogenesis

Even when alveolar rupture does not occur, excessive tissue stresses are damaging, whether produced by positive or negative pressure. Patients with ARDS ventilated with high plateau and driving pressures are at
highest risk for ventilator-induced lung injury (VILI), but recent work advocates a lung-protective approach for most patients who receive positive pressure ventilation. In experimental animals, the choice of ventilatory pattern dramatically influences the morphology of normal and previously injured tissues. Such findings are not surprising, given that repeated tissue overstretching and repeated tidal recruitment and collapse initiate inflammatory mechanosignaling—more than 20,000 tidal cycles are undertaken each day.

**Components of the Pressure Balance**

- \( P_D \) and \( P_{PLAT} \) are end-inspiratory pressures with and without flow during a pause.
- \( P_{RES} \) is flow-resistive pressure loss during inflation.
- \( mPaw_i \) = mean inflation pressure, which is the inspiratory machine work per liter of ventilation.
- The difference between alveolar pressure and total PEEP drives expiration.
- \( mPAW_T \) = mean airway pressure for the entire cycle.

**FIGURE 8-4. Components of the airway and alveolar pressures during one volume-controlled breath with constant flow under passive conditions.** \( P_D \) and \( P_{PLAT} \) are end-inspiratory pressures with and without flow during a pause. \( P_{RES} \) is flow-resistive pressure loss during inflation. \( mPaw_i \) = mean inflation pressure, which is the inspiratory machine work per liter of ventilation. The difference between alveolar pressure and total PEEP drives expiration. \( mPAW_T \) = mean airway pressure for the entire cycle.

**Effect of Excessive Airway Pressures**

Ventilatory patterns that apply high transalveolar stretching forces cause or extend tissue edema and damage in experimental animals. These forces may be static or dynamic, and three components of the inflation cycle—the plateau, the PEEP, and their difference (the driving pressure, see below)—appear to influence the potential for injury (Fig. 8-4). The pressures required to overstretch delicate lung tissues were often encountered during traditional management of ARDS. Current evidence strongly suggests that static (“plateau”) airway pressures greater than 30 cm H₂O commonly produce regional overdistention when the chest wall is normally compliant, especially when end-expiratory pressure is too low to prevent widespread small airway collapse. Because of mechanical heterogeneity, overdistention of aerated units, opening and closure of unstable units (so-called “atelectrauma”), and powerful shearing forces may coexist in a geographically confined microzone (Fig. 8-5). Forces multiply at the junctions of closed and open tissues, which are dispersed throughout the lungs, but these junctional
interfaces tend to be more numerous in dependent lung zones (Fig. 8-6). This regional proclivity results from the reduced transalveolar pressures associated with the hydrostatic forces attributable to lung weight and hence the tendency for collapse of marginal units (Fig. 8-7). The strong collagen infrastructure of the lung degrades unevenly, eventually predisposing to overt alveolar disruption (PTX, pneumomediastinum, gas cyst formation). Independent of radiographic evidence for extra-alveolar gas, however, the lung may sustain edematous injury (VILI) produced by high tissue strains during inflation and the associated driving power delivered to the lung.

**FIGURE 8-5.** Damaging forces during ventilation of the mechanically heterogeneous injured lung. **A:** The tangential shearing forces at the junction of expanding and collapsed alveolus may far exceed the tensions experienced in the free walls of expanding units, especially at high inflation pressures. **B:** When stress focusing causes junctional tensions to rise high enough, the resulting shearing action may exert sufficient force to cause damage to basement membranes and interstitial micro-elements, as well as capillary stress fractures and hemorrhagic edema.

**FIGURE 8-6.** Spectrum of forces at the interface between closed and open lung units. In the junctional
zone between inflated and collapsed tissues, lung units within a relatively small geographic region (highlighted
and expanded in the schematic) simultaneously may have noninflated units (A), overdistended units (B), and
stress focused units under high strain (C). Note the topological distribution of tissue density, which predominates
in dependent zones.

FIGURE 8-7. Gravitational gradients of increasing pleural and decreasing transalveolar pressures and
their influence on the airway pressure tracing inscribed during passive inflation with constant flow. D, dependent; EXP, expiration; INSP, inspiration; ND, nondependent.

A well-conducted, multicenter comparative clinical trial of moderately high (12 mL/kg of predicted body weight)
and relatively low tidal volume (6 mL/kg) in patients with ARDS by the NIH-sponsored ARDS network showed a
decided survival advantage for the lower tidal volume limb. Because tidal volumes much higher than this can be
applied without injuring healthy lungs (e.g., during exercise), it is logical to assume that it is the pressures
required to force larger tidal volumes into damaged lungs with reduced aerating capacity that overstrains
individual lung units, mediating the adverse response. Analysis of the data from large clinical trials uncovered
that plateau pressure correlates much better than tidal volume with mortality risk, even when adjusted for
disease severity. Any reduction of pleural pressure during spontaneous breathing raises the transalveolar
pressure, so that a plateau airway pressure obtained under these conditions may seriously underestimate VILI
risk. Moreover, although tidal volume is most usefully related to aerating capacity (as indexed by transpulmonary
pressure or ideally measured by end-expiratory lung volume), it might also be important for other reasons. The
magnitude of tidal volume relates to the pressures flow and energy necessary to drive it. Flow itself may have a
powerful influence on the expression of injury resulting from any given peak alveolar pressure or driving
pressure, as it is a prime determinant of shearing force. Moreover, higher tidal volumes are associated with
higher expiratory flows that may help disseminate airway biofluids, accentuating injury propagation (see
“Propagation of Lung Injury by Ventilation Pattern and Positioning,” following).
FIGURE 8-8. Relationships among plateau pressure, PEEP, and their difference (driving pressure).

Highly vulnerable junctional lung tissues are depicted as the yellow zone. Separation between $P_{PLAT}$ and PEEP extends the lever arm associated with potential for ventilator-induced lung injury. Note that the same plateau pressure may be associated with greater or lesser risk for VILI, depending on the associated driving pressure.

Although there now remains little question that high inflation pressures are damaging, their impact is likely to depend not only on the number of collapsed and unstable units but also on the associated *driving pressure* defined as the difference between end-inspiratory plateau and PEEP obtained under passive conditions (Fig. 8-4). This difference between two static pressures can be thought of as the “lever-arm” for shearing stress at the junctions of closed and open tissues (Fig. 8-8). An important analysis of the factors associated with mortality in ARDS concluded that the strongest predictive variable associated with the breathing cycle was driving pressure, the pressure difference equivalent to tidal volume ($V_T$) divided by respiratory compliance ($C_{RS}$). Surprisingly, these population-based data suggest (but do not prove) that a driving pressure of fixed magnitude may hold similar potential for injury, independent of the plateau and PEEP that determine it (Fig. 8-9). Driving pressure appears to be especially hazardous when $>15$ cm H$_2$O and the chest wall is normally compliant. H$_2$O. The causal role for high driving pressures in VILI is supported by numerous experimental studies, but the exact mechanism by which VILI itself increases mortality risk has not been clinically established. Setting exact safety limits for plateau pressures is not an easy task, being complicated by the contributions of multiple cofactors of varying importance and difficulty of measurement (e.g., rate of alveolar pressure development, interstitial pressure, and microvascular pressure gradient). The transalveolar stress that develops in response to building airway pressure is influenced by the relative compliances of the lung and chest wall. Although an imperfect indicator of the interstitial pressure that surrounds the airspaces of the injured lung, intrapleural pressure is believed to be a reasonable estimate. Measurement of esophageal pressure ($P_{es}$), therefore, may be prudent, therefore during vigorous breathing or when plateau pressures higher than 30 cm H$_2$O are contemplated and the chest wall is suspected to be stiffer than normal, as in the setting of abdominal
hypertension (e.g., ascites, extreme obesity, recent surgery). Transalveolar driving, end-expiratory, and plateau pressures are the true variables of interest in VILI prevention. A bladder pressure measurement is a noninvasive means of estimating intra-abdominal pressure, which when elevated may indicate the advisability of measuring esophageal pressure (see Chapter 5).

FIGURE 8-9. Same driving pressure applied at two levels of PEEP. In this analogy, PEEP is the fulcrum of a balance whose lever arm is the driving pressure. The yellow tissue area represents dependent collapse and consolidation. Some analyses of clinical data relating mortality to ventilator strategy suggest that VILI risk from a given driving pressure may be independent of the pressure range over which it is applied.

Importance of End-Expiratory Lung Volume and PEEP

Failure to preserve a certain minimum end-expiratory transalveolar pressure (i.e., total PEEP) in the early phase of ARDS may intensify preexisting alveolar damage, especially when high inflation pressures are used (see Chapter 9 for a detailed examination of PEEP). As already noted, tissue stresses are amplified at the junctions of closed and open lung tissues (a process known as "stress focusing"), and the magnitude of these forces is conditioned by the alveolar pressure. Indeed, these high-magnitude forces may initiate mechanosignaling of inflammation or produce shearing effects associated with repetitive collapse and reinflation of injured alveolar tissues. These risks on unrecruited are dramatically increased by raising the plateau pressure, which independently of its amplification of stress focusing tends to increase the hazards associated with lung stretch and energy load (see below). Together, these phenomena may be responsible for an important component of ventilator-induced lung damage (Fig. 8-10). Extreme forces cause rupture of delicate membranes, hemorrhage, and inflammation; repeated stresses of even moderate amplitude may cause mechanosignaling of inflammation (Fig. 8-11). The end-expiratory pressure required to avert widespread alveolar collapse varies with the hydrostatic forces applied to the lung; consequently, a higher end-expiratory pressure is required to prevent atelectasis in dependent regions than in the more superior zones (Fig. 8-7). Gravitational factors, therefore, help to partially explain the strikingly dependent distribution of radiographic infiltrates shortly after the onset of lung
injury, as well as the reversal of these infiltrates and improved arterial oxygenation in the prone position. Experimentally, prone positioning has been shown to even the distribution of ventilation and to avert much of the ventilator-associated lung injury occurring in dependent areas. Applying PEEP sufficient to position the tidal volume above the point of widespread lung unit closure attenuates severe hemorrhagic edema otherwise induced in laboratory animals by high ventilating pressure. Avoidance of stress-focused lung damage because of alveolar microcollapse and high driving pressures is a fundamental objective of strategies for lung protection, such as APRV (see Chapter 7).

![Diagram of PEEP, plateau, and driving pressures](image)

**FIGURE 8-10.** Conceptual interrelationship of PEEP, plateau, and driving pressures to recruitment and potential for VILI. Within the lungs, *horizontal lines* indicate prevalence of high stress interfaces between closed and open lung units, and *unfilled circles* indicate alveolar overdistention. Increasing driving pressure (A) to (B) accentuates damage potential. Raising PEEP for same high plateau pressure (C) reduces the driving pressure and damage potential but may increase number of overdistended lung units.

In a laboratory setting, inflicting severe lung damage requires both the application of high pressure and failure to maintain recruitment with sufficient end-expiratory pressure. Very high pressures are required to open refractory lung units, but once opened, considerably lower values of PEEP can keep those same units from collapsing (see Chapter 5). Pressures that recruit some lung units are likely to overdistend others. (This principle is illustrated in CT comparisons of dependent and nondependent zones.) Unless the lung is kept open by sufficient PEEP, widespread transient lung recruitment is likely to occur during each cycle of tidal inflation. Fortunately, the majority of (but not all) lung units can be kept open by PEEP levels well below 20 cm H$_2$O, provided that the compliance of the surrounding chest wall is relatively normal (Fig. 8-12). Although most unstable lung units of a patient with ARDS have opening pressures of less than 25 cm H$_2$O, refractory lung units may require sustained opening pressures that exceed 60 cm H$_2$O. This requirement provides a rationale for incorporating recruiting maneuvers.
into the ventilation strategy for these patients. In some centers, attempts are made to maintain recruitment of the great majority of unstable lung units—the "open lung" approach (see Chapter 24). Convincing arguments can be mounted both in favor of and in opposition to this strategy (Tables 8-4 and 8-5).

**FIGURE 8-11.** A hypothetical schema of the mechanisms by which ventilatory stress/strain result in inflammation.
FIGURE 8-12. Histograms of opening and closing pressures of the injured lung, expressed as percentage of recruitable alveolar units in ARDS patients. Note that the curve describing closure is left shifted, indicating that less pressure is needed to prevent derecruitment (closure) than to open those same recruitable units (opening).

Table 8-4. Why Should We Consider Aggressive Recruitment ("Open Lung") Strategies?

- Improved gas exchange
- Regenerate surfactant
- Less ventilator-associated pneumonia
- Reduced VILI hazard (in highly recruitable lungs)
- Lower risk of decompartmentalization (in highly recruitable lungs)
  - Gas
  - Bacteria
  - Inflammatory mediators

Stress failure of normal pulmonary capillaries with resulting extravasation of formed blood elements into the interstitium and alveoli may occur at transvascular pressures that exceed 40 to 90 mm Hg, depending on the animal species. Transcapillary mechanical forces of comparable magnitude may be generated when high tidal airway pressures are applied to diseased, heterogeneous lungs. High vascular pressures and blood flows also
may be important determinants of lung injury (Fig. 8-13). The breakdown of the alveolar-capillary barrier may create a portal for air, bacteria, and proteinaceous debris to enter the systemic circulation. Vascular pressure appears to be only one of many important cofactors that influence the expression of VILI. Apart from vascular pressure and body position, high inspired fractions of oxygen may contribute by their direct toxic effects or by encouraging absorption collapse. Experimental VILI-associated inflammation may be intensified by fever and attenuated by hypothermia.

**Table 8-5. Why Should We NOT Attempt to Fully “Open” The Lung?**

<table>
<thead>
<tr>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injured lungs may not be highly recruitable</td>
</tr>
<tr>
<td>• Recruitability may be limited to early phase</td>
</tr>
<tr>
<td>ARDS is a heterogeneous condition</td>
</tr>
<tr>
<td>• Some areas will be overstretched as others open</td>
</tr>
<tr>
<td>• Higher mean airway pressures increase stress focusing and global strain</td>
</tr>
<tr>
<td>Overdistended lung zones generate “Zone 2” conditions</td>
</tr>
<tr>
<td>• Dead space</td>
</tr>
<tr>
<td>• VILI (because of vascular stress)</td>
</tr>
<tr>
<td>Lung opening has a pressure cost and hazard</td>
</tr>
<tr>
<td>• Hemodynamic compromise</td>
</tr>
<tr>
<td>• Heightened tissue strain</td>
</tr>
<tr>
<td>Clinical trials are not consistently supportive</td>
</tr>
</tbody>
</table>

**Importance of Delivered Energy, Power, and Minute Ventilation**

As currently implemented, lung-protective ventilation concentrates on certain static characteristics of the individual tidal cycle—tidal volume (TV), plateau pressure, PEEP, and on the difference between the latter two static values, the driving pressure. Excessive stretch, strain, opening, and closure may all be important, but the precise mechanism through which they act remain unclear. Damaging forces require energy, and the energy delivered per unit time (“power”) has been suggested to be a unifying variable into which most ventilator settings and forces relevant to VILI can be channeled, thus providing a possible “composite index” of bedside-adjustable components (TV, RR, ΔPaw, PEEP, I:E, flow). This interesting and provocative proposal urges a potentially important conceptual shift in our thinking about VILI. The total inflation pressure ($P_{TOT}$) corresponding to any volume ($V$) above the fully relaxed value (FRC) must be accounted for in the sum of dissipated and conserved pressures, usually approximated as the simplified equation of motion:

$$P_{TOT} = \text{flow} \times R + \frac{V}{C} + P_{EEP_{TOT}} \text{ (Fig. 8-4)}.$$  

The energy expended during passive ventilation—the work of each tidal inflation—is the product of the proximal airway pressure and the volume change it produces. This inflation energy per cycle and its subcomponents that relate to resistance, driving pressure, and PEEP can be depicted as a pressure-volume plot (Fig. 8-14). Power or energy load, defined as work per unit time, takes the number of energy cycles per minute (breathing frequency) into account. The most relevant component of the pressure delivered to the lung per breath is $V_T / C$ or driving pressure ($P_{plat} - \text{PEEP}$). The driving energy per breath is $DP \times V_T$. The product of $DP$ and $[V \text{ with dot above}]_E$, adjusted for the reduced capacity of the ARDS lung, has been termed the driving power. Knowing that enormous power is expended during the heavy exertion of strenuous exercise, the ability of driving power to
damage, however, is likely to be limited until the maximal stress exceeds certain threshold values for plateau and driving pressure.

FIGURE 8-13. Potential contribution of vascular transmural pressure to lung edema and VILI.

The proposition that power, size-adjusted to account for the “baby lung” of ARDS, relates directly to VILI has intuitive appeal. Experimental studies have shown that although the peak magnitudes of tidal alveolar stresses and strains are very important, other factors condition the resulting damage. The excursion of tidal pressure (DP) appears at least as important as the maximum (plateau) pressure applied, and the frequency of potentially injurious cycling helps determine tissue damage. Flow rate and profile, clinically adjustable variables often deemphasized in the lung-protective strategy, have also been shown influential, even when plateau and driving pressures remain constant. The alluring aspects of this “VILI-Power” hypothesis are several. In accounting for key dynamic (as well as static) variables, it lends mechanistic plausibility to the observation that DP is more influential than plateau pressure. If damage resulted from excess power delivery, it would not depend exclusively on the maximal (plateau) pressures achieved during the individual tidal cycle but rather on the entirety of the inspiratory pressure excursion (DP) and on the frequency of its application. What is more, these contributing components of the power equation are quantified, ranked, and condensed into a single practical index with potential to guide machine adjustments at the bedside.
Raw power or even driving power may prove too simplistic. Most power delivered to the lung is stored temporarily in the respiratory system during inflation and then released during exhalation. Some power, however, is expended within the lung itself in reversibly deforming tissue, overcoming viscoelastance and surface tension, recruiting unstable units, displacing blood, etc. Perhaps the product of cycling frequency and the hysteresis area enclosed within the tidal transpulmonary pressure-volume loop—a PEEP and recruitment-influenced variable that quantifies the lung-dissipated energy per cycle—may enhance and refine the power principle in the attempt to home in on the true proximate mechanical cause of VILI. Emphasizing the “ergotrauma” of delivered power calls attention to the often neglected mandate to reduce the demand for ventilation as well as the dynamic stress imposed by each individual tidal breath.
FIGURE 8-15. Principle of progressive loading of parallel load-bearing elements with potential for accentuated strain (stress focusing) and materials failure. As weak elements are broken, stress becomes amplified for those elements that remain to bear the unchanging total load.

Finally, the proximate mechanical cause of VILI might relate only indirectly to energy load, power, and driving power. Repeated application of excessive strain may cause weak and vulnerable stress bearing elements to break, thereby increasing the stress and strain on those microfibers that remain intact to bear the load (Fig. 8-15). This second “progressive loading” form of stress focusing might cause local materials failure and wounding of the lung’s microstructure.

Propagation of Lung Injury by Ventilation Pattern and Positioning

The diffuse injury that characterizes ARDS is often considered a process that begins synchronously throughout the lung, mediated by inhaled or blood-borne noxious agents. Relatively little attention has been paid to the possibility that inflammatory lung injury may also begin focally and propagate sequentially via the airway network, proceeding mouthward from distal to proximal. Were this true, modifications of ventilatory pattern and position aimed at geographic containment of the inflammatory injury process could help prevent its generalization and limit disease severity. If airway propagation of proteinaceous, mediator-laden edema plays an important role in disseminating injury, which would be the key elements of a lung-protective ventilation strategy targeted to that specific aspect? (Table 8-6). In the earliest (edematous) stage of lung inflammation (perhaps the first 48 hours), when airway biofluids are mobile, logical steps would include relatively high PEEP to encourage edema to stay at its site of origin or translocate to the interstitial space, to use small tidal volumes to reduce the peak expiratory flows that drive
airway fluid mouthward, to minimize minute ventilation (to avoid larger tidal volumes and expulsive expiratory efforts), to avoid fluid excess and edema, to dependently orient the most involved segments or lobes, and to silence vigorous expiratory effort (Fig. 8-16).

Table 8-6. What Makes Mucus and Edema (Biofluids) Move Within the Airway?

- Biofluid volume
  - Antibiotics
  - Steroids
- Biofluid consistency
  - Hydration, mucolytics, β-agents, lubricants
- Exhalation time constant
  - ↓ Expiratory resistance
- Ventilation pattern
  - ↑ $V_T$ ↓ Inspiratory flow ↓ PEEP help expel
- Adjuncts to secretion clearance
  - Position, vibration, in-exsufflation
FIGURE 8-16. Factors that encourage or prevent intra-airway transfer of biofluids between diseased and normal lung. Nondependent positioning, high PEEP, and low driving pressures may be “lung protective” in this setting.

Early intervention would be vital in trying to limit transairway propagation of noxious biofluids during their high mobility phase. Later on,

when gelling has occurred, the positioning priority shifts to expulsion of the thickened secretions, which otherwise act to plug airways rather than to propagate disease. With fluids relatively immobile or neutralized, PEEP gradually loses its value in preventing airway flooding. Although there is little doubt that certain postural reorientations encourage airway drainage and should be strongly considered when it is safe to do so, it is sobering to think that side-to-side repositioning undertaken from the first hours of care to prevent skin breakdown might actually help to distribute noxious lung fluids more widely into previously unaffected zones before gelling inhibits secretion mobility. Moreover, bacteria contained in situ are neutralized over time by immune defenses and/or antibiotics. After the first few days, clearance of thickened mucus (rather than prevention of spread of
mobile liquid) assumes therapeutic primacy. 

Propagation avoidance measures do not contradict the basic elements of the “low tidal volume/open lung” approach to lung protection but, rather, extend their rationale. Such questions as whether altering the ventilatory prescription, position, or their combination could contain (or conversely amplify) an initially focal injury process seem especially attractive to explore. In the earliest phase of acute lung injury (ALI) and lobar pneumonia, it is rational to employ a recruiting strategy and generous PEEP so as to contain highly mobile thin fluids within the minimal number of segments.

**Links Between VILI and Dysfunction of Systemic Organs**

Intriguing laboratory and clinical data have shown that inflammatory mediators originating in the lungs of patients with ARDS may translocate to the periphery when high inflation pressures and reduced levels of PEEP are utilized. Such observations suggest possible but unconfirmed links between ARDS, ventilating pattern, and the associated multisystem organ failure that accounts for the deaths of many patients ventilated for this disorder. Although dysfunctional initiation of inflammation by circulating signaling mediators is an attractive hypothesis, just how lung inflammation incites remote injury is a current research topic of intense interest. It must be emphasized that we do not yet know the exact mechanistic link between ventilator strategy, VILI, and mortality risk.

**Management**

Detailed guidelines are not available regarding the maximum safe peak, mean, and driving alveolar pressures that can be applied for extended periods without inducing alveolar damage or retarding lung healing. Clearly, the answer differs among individual patients. Alveolar stresses undoubtedly vary with PEEP and position and differ from site to site within the damaged lung (Fig. 8-8). The airway pressure applied to the endotracheal tube (ET) must account for the distensibility and vulnerability of each type of lung unit. It is generally agreed that lower driving pressures and plateau pressures are safer regarding VILI. If the chest wall is normal, these should not be raised above 15 and 30 cm H₂O, respectively, during passive inflation (and less if the patient is actively breathing). Although failure to preserve a certain minimum end-expiratory transalveolar pressure has been shown experimentally to intensify preexisting alveolar damage when end-inspiratory alveolar (plateau) pressure is high, this phenomenon has not yet been convincingly demonstrated in clinical trials. When combined with a small tidal volume, higher PEEP did improve mortality outcome in a several studies of moderate size. However, the larger ALVEOLI trial of the ARDS network did not show a clear advantage in its higher PEEP limb. (The design of that trial did not allow application of high alveolar pressures to patients of either group.) Similarly, the large Canadian LOVS and French EXPRESS trials demonstrated some intriguing advantages for their higher PEEP patients but no clear mortality advantage overall (see “Suggested Readings” in Chapter 9). Once recruitment has been almost completed, additional PEEP is probably ineffecutal or damaging. Consequently, expert opinion differs regarding whether applying the least PEEP that accomplishes adequate gas exchange, setting PEEP for best compliance, or guaranteeing some minimal value of end-expiratory alveolar pressure is the best course to follow during the first few days of the disease process. Initially sustained application of high inflating pressures to recruit unstable lung units (recruiting maneuver) followed by decremental setting of PEEP continues to be advocated by knowledgeable investigators, especially when small tidal volumes (<4 to 5 mL/kg) are used or when HFV is employed (Chapter 9). PEEP should be withdrawn later in the disease process if no important deterioration of gas exchange or mechanics occurs upon its reduction.

### Table 8-7. Contraindications to Permissive Hypercapnia
Increased intracranial pressure  
Severe cardiovascular dysfunction  
Severe pulmonary hypertension  
Profound metabolic acidosis  

At FiO<sub>2</sub> levels less than 0.7, limiting \( P_{aw} \) to “safe” levels generally takes precedence over limiting FiO<sub>2</sub>. Allowing PaCO<sub>2</sub> to rise to supernormal values (permissive hypercapnia) is an effective strategy for limiting ventilating pressure (see Chapter 24). The full effects of hypercapnia on such important variables as gas exchange, cardiovascular dynamics, and tissue edema are yet to be described in the two settings for which it is most commonly applied—asthma and ARDS. Moreover, there are both relative and absolute contraindications for using this technique (Table 8-7).

**SUBACUTE AND CHRONIC COMPLICATIONS**

**Fluid Retention and Redistribution**

Extravascular fluid retention tends to develop during positive pressure ventilation for several reasons: (1) ventilated patients are relatively immobile; (2) as increased intrathoracic pressure limits venous return, stretch receptors located in the atria signal additional antidiuretic hormone (ADH) release to help replenish central vascular volume; and (3) hypotension induced by positive pressure may curtail renal perfusion, redistribute renal blood flow, reduce glomerular filtration, and promote sodium and water retention. PEEP may cause a similar redistribution of intrarenal blood flow by reflex mechanisms. The hypoalbuminemia almost routinely present in the ventilated, critically ill patients also contributes. When positive pressure ventilation is abruptly discontinued, these fluid shifts reverse and may encourage cardiac decompensation in patients with poor reserve, as fluid translocates from extravascular sites to the central vessels.

The controversy regarding fluid management in ARDS (liberal vs. restricted) is more than an academic one; published data convincingly indicate that fluid retention correlates with adverse outcomes, either because tissue edema is a marker of disease severity or because it relates integrally to organ dysfunction. Whether colloid (e.g., albumin) or crystalloid (if so, which one?) should be favored as a resuscitation fluid is a controversy that has raged for years. Currently, crystalloid seems to hold the advantage, but as with most such debates, the answer may vary with the detailed physiology of the individual case.

**Fluctuations in pH**

The ventilator can powerfully affect acid-base balance. When support is initiated, special care should be exercised not to reverse acidosis too quickly or to cause marked respiratory alkalosis. Metabolic alkalosis tends to develop in mechanically ventilated patients because of intravascular volume contraction, nasogastric suctioning, or use of steroids. If repletion of chloride and intravascular volume fails to correct it, acetazolamide (Diamox) may help eliminate excess fluid while dumping surplus bicarbonate. In the assist/control mode, marked fluctuations in pH and PaCO<sub>2</sub> can occur in patients who are alternately agitated and sedated, especially if the ventilator’s backup rate is inappropriately low. Mental status and ventilation mode always should be taken into account when interpreting blood gas values.

**Infections**

Infections of the lung and upper respiratory tract are exceedingly common during mechanical ventilation.
Liquid within corrugated ventilator tubing allows bacteria to multiply. Therefore, care should be taken to prevent transfer of any condensate into the trachea during manipulations of the ventilator circuit or changes of patient position. Indeed, such transfers have been suggested to, at least partially, explain why pneumonia seems to occur more frequently among patients who undergo frequent changes to fresh ventilator circuits. Nasotracheal and nasogastric tubes encourage sinus infection by blocking their ostia, which prevents drainage. In itself, occult sinusitis may cause febrile episodes in intubated patients. Furthermore, blocked sinuses also provide a seeding focus for infections of the lung and bloodstream.

**Ventilator-Associated Pneumonia**

Continued intubation of the airway strongly predisposes to hospital-acquired pneumonia, a serious problem associated with increased morbidity and mortality. Ventilator-associated pneumonia (VAP) is a term generally reserved for infections that develop by 48 hours or more after mechanical ventilation is initiated. It is now certain that patients receiving noninvasive ventilation by pressurized face mask have an impressively lower incidence of VAP. Heavy sedation and damaging ventilatory patterns are less likely to be applied during noninvasive ventilation (NIV) because of the inherent pressure limitations of the noninvasive approach. However, the most intuitive reasons for NIVs relative advantage reside in preservation of clearance mechanisms and prevention of lower airway inoculation.

The oropharynx teems with microbes, but in healthy persons, the upper airway normally remains relatively sterile below the vocal cords, swept clean by the mucociliary escalator, and protected by an effective cough. Bypassing the upper airway with an ET seriously impairs these defenses while facilitating inoculation of the lower airway and lungs with high concentrations of potential pathogens. The rate of developing VAP is strongly influenced by institutional practices such as handwashing, good oral hygiene, and inclining the head of the bed to 30 degrees or more. On average, it approximates 2% to 3% per day. Overt pneumonitis usually manifests with gram-negative hospital-acquired organisms after the first week of hospitalization. Because all new infiltrates are not necessarily pneumonia and because the pathogen may not be obvious, bronchoalveolar lavage (BAL) is quite helpful in establishing the correct diagnosis. Poor dentition, impaired nutritional status, age, immobilization, immune compromise, and the supine position predispose pulmonary infection (Table 8-8). Once under way, pneumonia contributes clearly to the mortality resulting from such underlying conditions as decompensated chronic obstructive pulmonary disease (COPD) and ARDS. Preventative measures include head-up body positioning, tooth brushing, and chlorhexidine mouth hygiene (see Chapter 18).

<table>
<thead>
<tr>
<th>Table 8-8. Predispositions to VAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinusitis</td>
</tr>
<tr>
<td>Poor dentition</td>
</tr>
<tr>
<td>Immobilization</td>
</tr>
<tr>
<td>Immune compromise</td>
</tr>
<tr>
<td>Supine position</td>
</tr>
<tr>
<td>Coexisting nasogastric tube</td>
</tr>
<tr>
<td>Lengthy period of ventilation</td>
</tr>
<tr>
<td>High gastric pH</td>
</tr>
<tr>
<td>Condensate within ventilator tubing</td>
</tr>
<tr>
<td>Frequent circuit disconnections</td>
</tr>
<tr>
<td>Poor endotracheal cuff seal</td>
</tr>
</tbody>
</table>
Risk Factors for VAP

Although pneumonia occasionally arises from hematogenous inoculation, most alveolar seeding occurs via the airway. In epidemiologic and experimental studies, the likelihood of developing pneumonia relates to the size of the infective inoculum and the effectiveness of secretion clearance. The ET interferes with the mucociliary escalator and with coughing effectiveness. Colony counts of oral secretions may exceed $10^8$/mL, and a rich pool of such fluid often collects above the ET cuff. Aided by gravity, the interstices of the ET cuff may allow continuing seepage of these secretions into the lower airway. Axial movement of the ET may help deliver a critical inoculum into the lower airway. ETs that allow aspiration of the supraglottic pool are associated with lower incidence of VAP. Adding to the infection risk, sinus drainage is seriously impaired by extended immobility in the supine position. Oral tubes compromise mouth closure and secretion cleansing. On the other hand, nasal tubes allow mouth closure but impede ipsilateral sinus drainage and increase the reservoir of nosocomial pathogens at risk for aspiration. Frequent breaks, ventilator circuit change, and tubing condensate (“rain out”) predispose to lower airway seeding. Nasogastric and orogastric tubes encourage bacterial overgrowth and aspiration, especially in the supine position. Although there is general agreement that the head of the intubated patient should be elevated at least 30 degrees, how importantly gastric feedings and antacid therapy contribute to the pneumonia risk is still a matter for debate. An intriguing body of experimental and clinical data suggest not only that high tidal volume and low PEEP ventilatory patterns predispose to the lung damage but also that lungs injured in this fashion are unusually susceptible to pulmonary infections. Moreover, in varied animal models, such patterns cause capillary rupture and allow bacteria, inflammatory products, or mediators to enter the bloodstream.

Diagnosis and Treatment of VAP

Diagnostic techniques and approaches to management of VAP are detailed in Chapter 26. It should be emphasized here, however, that the diagnosis and management strategies for VAP are by no means straightforward. It is known that the bacteriology of the oropharynx and upper airway are different for otherwise healthy individuals recently admitted to the hospital, compared with already debilitated patients, and that colonization patterns shift as hospitalization time lengthens. Although fever, purulent sputum, and a new infiltrate certainly suggest the development of pneumonia, many commonly encountered conditions are associated with those same features, especially in intubated patients. Although air bronchograms and other features detected by CT scanning are highly suggestive, uncertainty often remains and precise bacteriologic diagnosis may be elusive. Sputum cultures are almost invariably positive for several potential pathogens in untreated patients after 2 days in hospital, because of tracheal colonization; moreover, atelectasis and edema can develop, confounding the radiographic features. Multiple organisms are frequently recovered from lung tissue of patients with suspected pneumonia. Techniques such as blind catheter lavage (mini-BAL, usually performed by respiratory therapists) and bronchoscope-directed lavage or protected specimen brushing of the suspected region improve the chances of accurate diagnosis. Such data may help modify empirical choices of antibiotic and therefore help prevent emergence of resistance or superinfection with more noxious pathogens, but it is unclear whether such tailoring confers a significant mortality advantage. Antibiotic treatment should begin soon after VAP is suspected, and selection of specific agents is best made considering the underlying medical and physiologic status of the patient, the time elapsed since hospitalization, whether the patient has recently been in a hospital or nursing home, susceptibility patterns of the organisms usually encountered in that specific ICU environment, and prior antibiotic treatment. The wisdom of giving a brief course corticosteroids once the diagnosis is made and inflammatory signs are present...
prominent has not yet been scientifically established or generally accepted into practice.

**Deconditioning and Diaphragmatic Dysfunction**

Weakening and discoordination are detectable within the first day of complete diaphragmatic rest as the work burden and breathing pattern are assumed by the machine during controlled ventilation. Severity of this ventilator-induced diaphragmatic dysfunction (VIDD) accelerates toward its nadir with passing days of inactivity. Such vulnerability of this vital pump is surprising but may relate to the fact that the diaphragm is the one skeletal muscle designed and conditioned for continuous use. As a rule, patients receiving assisted mechanical ventilation expend sufficient effort triggering the ventilator to prevent disuse atrophy, but it is unclear whether original muscle bulk and strength are fully preserved. The problem of deconditioning seems most serious for those patients who must assume a large workload of breathing when mechanical ventilation is discontinued, for those with preexisting neuromuscular impairment, for those with suppressed ventilatory drive, and for those requiring prolonged deep sedation and/or paralysis. Clearly, VIDD may contribute to delayed liberation from ventilatory support. Nutritional support, encouraging spontaneous activity (e.g., continuous positive airway pressure [CPAP] pressure support), and perhaps muscle training are likely preventative. It is conceivable (but unproved) that the daily interruptions of sedation and trials of spontaneous breathing that are now advocated for weaning assessment could help preserve bulk and strength, even during the acute stage.

**PATIENT-VENTILATOR INTERACTIONS**

**Specific “Early Phase” Problems**

*Poor Coordination Between the Breathing Rhythms of Patient and Ventilator*

Initial discomfort may be extreme because of the ET tube, distended hollow viscera, impaired swallowing, pharyngeal or sinus pain, anxiety, disorientation, inability to speak, or discomfort related to recent invasive procedures. Stimulation of bronchial, laryngeal, and carinal irritant receptors triggers bronchospasm and coughing efforts. Furthermore, mechanical ventilators usually are set to deliver higher (and occasionally lower) tidal volumes than the patient would choose spontaneously, whereas inspiratory pattern, flow rate, and cycling frequency differ from those of the presupport period. Hence, shortly after mechanical ventilation begins, attempts to “fight the ventilator” are the rule in alert, awakening, and mildly obtunded patients. Initial mismatching usually abates spontaneously (within minutes) as the settings are adjusted and the patient becomes accustomed to the machine. When deep sedation is not employed, constant bedside attendance by trained medical personnel is often necessary throughout this period, to calm the patient, adjust the settings to the patient's requirements, and ensure that the agitation neither interferes with gas exchange nor has a more serious origin. To ensure safety, it is extremely important to secure all tubing connectors and to appropriately restrain the arms of an intermittently agitated patient. Ventilator disconnection or self-extubation is a potentially lethal and distressingly common event, especially when nursing resources are stretched too thin. When the patient is connected initially, sensitivity should be adjusted so that the minimal effort avoids autocycling to trigger a ventilator breath. Pressure-targeted modes of ventilation (pressure control and pressure support) adapt automatically to the patient's changing flow needs and are often good choices to avoid dyssynchrony from flow mismatching. Pressure control breaths have a set duration, however, so that the I:E ratio varies when frequency changes. High-level pressure support is often helpful to determine the pressures and tidal volumes desired by the patient before switching to pressure or volume control. When either pressure control ventilation (PCV) or flow-controlled, volume-cycled ventilation is selected and minute ventilation is variable, synchronized intermittent mandatory ventilation (SIMV) may be better tolerated than...
assist control (see Chapter 7). Pressure (in PCV) or inspiratory flow rate and waveform (in flow-controlled ventilation [VCV]) is adjusted to a level commensurate with the vigor and frequency of the patient's efforts (see Chapter 7). Although high-level pressure support is generally effective in achieving adequate synchrony and comfort, very agitated patients may require temporary disconnection of the circuit and manual use of a self-inflating anesthesia bag. With the machine properly adjusted, mechanical malfunctioning ruled out, the patient examined, the initial set of blood gases analyzed, and the chest radiograph checked for position of the tube tip and PTX, an opiate complemented when necessary by benzodiazepine, dexmedetomidine, propofol, or ketamine may be given to assure continued smooth linking of endogenous respiratory and ventilator rhythms. Intratracheal lidocaine (2 to 4 mL of 1% to 2% concentration) can briefly arrest coughing spasms and reduce pain. A nasogastric or orogastric tube helps initially to decompress the gastrointestinal tract and is particularly helpful for patients with gastrointestinal motility impaired by opiates or disease who swallow air around orotracheal tubes. These tubes later serve as an enteral pathway for drugs and fluids.

**Special Problems of Patients with High Ventilatory Requirements**

Patients with high ventilatory requirements may overtax circuit valving or even the capacity of the ventilator to deliver gas at an adequate rate. Asynchrony markedly elevates the breathing workload, and tachypnea accentuates the importance of resistance within the ET and other circuit elements. Active use of the expiratory musculature may cause hypoxemia by combating the volume recruitment effect of PEEP, altering ventilation-perfusion relationships, and desaturating mixed venous blood. Pulmonary transvascular pressures may be significantly higher during active inspiration, as the interstitial pressure that surrounds the microvessels may dip impressively, promoting edema formation (Fig. 8-17). In these circumstances, reducing active effort can improve arterial oxygenation. Although deep sedation and paralysis can be helpful, prolonged immobility encourages regional atelectasis and secretion retention (especially in dependent areas), as well as muscle atrophy. For the paralyzed patient, ventilator disconnections can be rapidly lethal.

**Dyssynchrony**

Poor coordination between the patient and the ventilator regarding initiation, power assistance, and termination of breathing cycles, termed dyssynchrony or asynchrony, has been a common problem for traditional modes of ventilation. Several forms of asynchrony are illustrated in Figure 8-18.

Whereas time-cycled modes (e.g., VCV or PCV) are most susceptible to these timing issues because of their fixed inspiratory cycle lengths, pressure support ventilation (PSV) is not immune to them. Flow delivery that is inadequate or excessive to patient demand is possible with either flow regulated (VCV) or fixed pressure targeted (PCV, PSV) forms of support. It should be understood that the frequently used term “flow starvation” is a misnomer, in that any time a positive airway pressure above the baseline, the machine is aiding inflation. Newer modes that do not target a physician-set pressure, flow, or tidal volume, do not have a fixed trigger for expiration onset (e.g., proportional assist ventilation [PAV]), and/or are geared to phrenic nerve activity (neurally adjusted ventilatory assist [NAVA]) are less susceptible to these cycling conflicts and much better in avoiding dyssynchrony of inspiratory flow (see Chapter 7). Dyssynchrony represents more than inconvenience and discomfort, as recent studies demonstrate that duration of mechanical ventilation, sleep quality, and need for tracheostomy are adversely influenced by it. Published analyses suggest a significant association between asynchrony and mortality risk, although its causal role has not been confirmed. Clusters of asynchronous breathing may have worse prognostic import than asynchronous breaths that are more dispersed.
FIGURE 8-17. Impact of passive versus active breathing on the transmural forces across the lung and pulmonary capillaries. Lung dimensions are all the same, as are transpulmonary pressures. Transvascular pressures are different, however, as reflected by the diameters of the red “targets” that represent the pulmonary blood vessels.
FIGURE 8-18. Examples of common asynchronies between neural and machine timing rhythms.

Triggering dyssynchrony can be classified as autotriggering, ineffective triggering, and double triggering. Autotriggering usually results from a combination of a highly sensitive trigger setting and a circuit problem—condensation, secretions, vigorous cardiac oscillations, or (when flow triggering is used) a gas leak. Fixing sources of circuit “noise,” decreasing trigger sensitivity, and/or switching to the pressure triggering option usually correct autotriggering problems. A surprisingly common variant of triggering that is not initiated by the patient appears to be a consequence of positive neural feedback—possibly reflex initiated in response to the inflation stimulus of a passively initiated breath. It has been termed “reverse triggering” and when detected usually occurs against the background of unconscious sedation (Fig. 8-19). Whether reverse triggering has any adverse implications is a subject of current investigation.

Ineffective triggering is usually the product of weak inspiratory efforts, a higher than needed pressure target level, or auto-PEEP. Resetting the trigger to greater sensitivity, reducing the level of pressure applied during PCV or PSV, and reducing auto-PEEP (e.g., by pharmacotherapy or secretion clearance) or
counterbalancing auto-PEEP with external PEEP usually resolve such problems.

FIGURE 8-19. Reverse triggering. In this well-sedated patient, there were no spontaneous triggering efforts. A: Decelerating volume-controlled ventilation. The onset of the automatic machine cycle elicited diaphragmatic contractions of decreasing amplitude during the first three cycles but not the fourth. B: This tracing of airway pressure and flow illustrates that the machine was triggering patient during pressure assist-control, a mode in which breaths are timed to begin automatically if not triggered. If the patient was initiating the efforts, that would have been made clear during the abrupt switch to pressure support, a mode that needs patient effort to initiate machine pressurization of the airway.

Double triggering is actually an expiratory off-switch dyssynchrony and results from the patient needing a longer inspiratory time than set. It is often observed when the tidal volume or support pressure is set to a low level for “lung protection” when the patient has a high ventilation demand, when edematous lungs that would be stretched by a periodic sigh if the patient were spontaneously breathing, or both. Attention has been drawn to the observation that an unintentionally greater tidal volume than set may accompany these double-triggered events, especially during pressure-controlled ventilation. Even though frequent double triggering might violate the
principles of lung protection, well-set alarms and careful bedside surveillance reduces that theoretical risk substantially. A temporary switch to pressure support may allow determination of the patient's desired timing and depth of breathing. A trial increase in support (raising the pressure setting or extending the inspiratory time) can also be helpful, provided that the applied pressure is not itself dangerous. When delivering a higher tidal volume is not effective, the problem may be that the level of support being given is actually excessive, mandating an empiric trial of reduced pressure, SIMV rate, or inspiratory flow. Again, clearance of retained secretions is potentially important. In this double-triggering situation, therapy is often empirical.

Problems with the expiratory off-switch sometimes arise during PSV. These can be premature termination or delayed termination of the inspiratory period. Convulsive initiation of the breath, as during hiccough, causes flow to fall precipitously and the machine to cycle off. Conversion to a time-cycled, pressure-targeted mode (PCV) is sometimes the answer. In the setting of airflow obstruction, the problem may be the opposite—cycles of excessive length that require active expiratory effort to terminate. Empirical adjustment of the expiratory trigger to a higher percentage of peak flow (e.g., from 25% to 50%) is usually helpful.

**Specific “Support Phase” Problems**

Smooth interaction between the patient and machine may be interrupted by malfunctioning of the ventilator system, worsening of cardiopulmonary mechanics, psychic distress, or factors completely unrelated to ventilation. Malfunctions of the ventilator system prevent adequate ventilation or oxygenation and usually present as agitation, worrisome changes in vital signs, or unexplained deterioration in blood gases.

**Diagnostic Approach to Agitation During Mechanical Ventilation**

When an event develops suddenly during mechanical ventilation, the clinician must efficiently diagnose the problem in an organized fashion. Many latest generation ventilators display helpful and explicit cues to action, such as “circuit disconnect.” When the problem is not quickly resolved, the patient should be ventilated manually with pure oxygen until the problem has been diagnosed. The difference between the exhaled versus set tidal volume may provide crucial data. A major difference unexplained by pressure limiting and “pop-off” losses indicates a circuit leak or machine dysfunction. Checking the airway pressure profile and comparing the peak dynamic ($P_D$) and peak static ($P_S$, or “plateau”) pressures against previous values also provide essential information. Failure to generate or hold pressure during circuit occlusion usually indicates a system leak. A large disparity between $P_D$ and $P_S$ suggests a resistance problem in the ET or airways (bronchospasm, secretions). It is useful to classify these problems as those that usually elevate peak cycling pressure (pressure limiting) and those that usually do not (Table 8-9). Three components of the system must be checked carefully: the patient, the tube, and the ventilator system.

<table>
<thead>
<tr>
<th>Table 8-9. Sudden Crises During Mechanical Ventilation</th>
</tr>
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<tbody>
<tr>
<td><strong>Pressure Limiting</strong></td>
</tr>
<tr>
<td>Central airway obstruction</td>
</tr>
<tr>
<td>Massive atelectasis</td>
</tr>
<tr>
<td>Tube occlusion</td>
</tr>
<tr>
<td>Mainstem intubation</td>
</tr>
<tr>
<td>Pain, anxiety, or delirium</td>
</tr>
<tr>
<td>Tension pneumothorax</td>
</tr>
</tbody>
</table>
Gas trapping (auto-PEEP) during VC ventilation  Pulmonary embolism
Irritative bronchospasm and coughing  Pulmonary edema (pressure-limited ventilation)
Decreased chest wall compliance
Secretion retention
"Flash" pulmonary edema

**Patient**

The importance of auscultation for signs of PTX, bronchospasm, secretion plugging, and pulmonary edema deserves emphasis. Mucus plugging, accompanied by major airway blockage, is a very frequent cause for sudden high pressures and hypoxemia. The symmetry of breath sounds and percussion dullness should be determined in one of the first steps of the evaluation. Among the most important distinctions to make is the one between massive atelectasis and tension PTX. A PTX that does not have a tension component may not elevate peak airway pressure (or reduce tidal volume) noticeably. Nonpulmonary causes of discomfort (distention of bladder or intestinal tract, unvarying body position, pain, etc.) are overlooked easily.

Problems occur frequently among patients with combined cardiac and pulmonary disease. Increased VO$_2$, heart rate, blood pressure, and left ventricular afterload can cause florid congestive failure ("flash" pulmonary edema), ischemia, or other manifestation of circulatory stress within minutes in a patient with coronary insufficiency or myocardial or valvular dysfunction. A quick glance at the cardiac monitor is mandatory. The sudden onset of a tachyarrhythmia, particularly driven by atrial fibrillation and atrial flutter, may be the primary driver of the distress. An ECG should be considered very early on if the problem is not otherwise quickly diagnosed and resolved. Quite often, adrenergic bronchodilator therapy is the culprit.

For patients receiving flow-controlled, volume-cycled ventilation (e.g., assist-control or SIMV), the need for increased minute ventilation often causes ventilatory demands to outstrip the ventilator's flow delivery and/or alters optimal breath duration and timing, increasing the work of breathing still further and setting into motion a self-perpetuating cycle of agitation and cardiopulmonary compromise. A boost in ventilatory support, switch to pressure-targeted ventilation, or adjustment of inspiratory flow rate often rectify the situation, but failing these, deeper sedation or even paralysis may otherwise be needed to assure lung protection and VILI avoidance.

A vicious cycle is especially likely to develop in agitated patients with airflow obstruction who hyperinflated, causing auto-PEEP with associated muscle dysfunction and hemodynamic stress. Both the work of breathing and dyspnea escalate markedly as the patient struggles to breathe. Temporarily switching to high-level pressure support (sufficient to achieve an effective tidal volume) often helps relieve dyssynchrony and dyspnea until the situation can be analyzed fully and the underlying cause can be addressed definitively. Disconnecting the ventilator and providing adequate ventilation manually with a resuscitator bag is an alternative strategy that frequently will break the cycle.

It must be stressed that once agitation develops, hypoxemia frequently occurs, increasing both the drive to breathe and dyspnea. Increasing the FiO$_2$ often reverses hypoxemia and can undo the self-reinforcing process of agitation → hypoxemia → increased drive → agitation → hypoxemia. In fact, increasing FiO$_2$ is a good first option whenever desaturation accompanies agitation. Although agitation often has a trivial origin, it must never be ignored or suppressed with sedatives until possible serious causes are considered. Bradycardia is experienced frequently during temporary machine disconnection for suctioning by patients requiring high levels of PEEP and mean airway pressure. Although hypoxemia occasionally is responsible for these episodes of bradycardia, this phenomenon usually is a reflex effect, which is prevented by pretreatment with systemic
atropine, “closed circuit” airway suctioning, or the provision of CPAP during secretion removal.

**Endotracheal Tube**

Modern ventilators are equipped with audible alarms that sense excessive or inadequate system pressure, failure to exhale a set minimum tidal volume, or disconnection of the patient from the machine. If the cause for distress is not immediately obvious, the caregiver should note the position of the ET in relation to its previously marked level, listen for cuff leaks during inflation (auscultate over the larynx), and palpate the pilot balloon to sense the pressure in the cuff. ETs often kink, block with secretions, or become constricted by the teeth of a biting patient. After assuring adequate oxygenation, a suction catheter is passed to check patency of the ET and aspirate central airway secretions. Vital signs are checked, and auscultation is performed quickly for evidence of PTX, massive atelectasis, or bronchospasm, as the patient is ventilated manually with 100% oxygen. Tubes that are poorly placed or secured may migrate into the larynx or right main bronchus or may rest on the carina, producing cough and bronchospasm.

**Ventilator Circuit**

The integrity of the ventilator circuit is inspected quickly, with special attention given to tubing connections and the settings for tidal volume, frequency, trigger sensitivity, and oxygen fraction. Both inspiratory and expiratory flexible tubing is checked for accumulated water, which may increase inspiratory resistance or cause inadvertent expiratory retard. Rarely, the swings and vibrations of airway pressure caused by retained secretions or circuit water are great enough to initiate autocycling. (When heat-moisture exchangers [HME] are used, these specific circuit issues are less common.) If the problem remains obscure, the patient can be reconnected briefly to check delivered versus set minute ventilation. If delivered minute ventilation is too low, all connections should be checked carefully for leaks, especially around the exhalation valve and humidifier, if present. In a passive patient, the application of an end-inspiratory pause will help detect a circuit leak. If the problem still persists, no cause is detected, and the chest radiograph is negative, judicious doses of an opiate (fentanyl or morphine) and/or sedative can be given, as long as gas exchange is well maintained as judged by oximetry or arterial blood gases. Pharmacoparalysis must never be undertaken until an alert patient is adequately sedated.

**Other Support Phase Problems**

Work of breathing, psychological distress, and depression are prevalent during mechanical ventilation and are discussed at greater length in Chapter 10.

**SUGGESTED READINGS**


Key Points

1. Adding positive end-expiratory pressure (PEEP) can help maintain functionality of unstable lung units but further expands those that are already patent. The former action usually is beneficial, whereas the latter may contribute to alveolar overdistention. Both effects may occur simultaneously in different lung regions at the same level of PEEP.

2. Positive end-expiratory alveolar pressure or total PEEP is the sum of the PEEP applied intentionally at the airway opening (PEEP or “extrinsic” PEEP) and auto-PEEP (“intrinsic” or “occult” PEEP) that results from dynamic hyperinflation. Expiratory muscle activity may raise the measured value for total PEEP.

3. Transalveolar pressure is the key variable that determines PEEP’s effect on lung volume. A patient with a poorly compliant chest wall, e.g., morbid obesity, will require higher PEEP to achieve adequate lung expansion.

4. Utility of PEEP in improving arterial oxygenation, in minimizing VILI, and perhaps in preventing pneumonia stems primarily from its ability to keep unstable lung units open. PEEP also improves the distribution of alveolar liquid, translocating edema fluid from the alveolus to the interstitium.

5. The volume-recruiting effect of PEEP is influenced by the chest wall compliance, the tidal volume, and the activity of the respiratory muscles. Any benefit from PEEP on oxygen exchange may be offset by end-expiratory muscle activity and restored by muscle relaxation.

6. A shift to the prone position exerts a selective PEEP-like action in the dorsal regions of the lung, evens the distribution of local transpulmonary pressures, reduces VILI risk, and commonly improves oxygenation of patients with lung edema.

7. PEEP tends to decrease both preload and afterload to the left ventricle. Impaired venous return may lower the cardiac output in a passive patient who does not have intact vascular reflexes or adequate circulating blood volume. The hemodynamic effects of auto-PEEP are similar to those of external PEEP.

8. High peak and mean alveolar pressures that result from excessive PEEP may increase the risk of lung injury, reduce oxygen delivery, and increase ventilatory dead space. PEEP may either increase or decrease the work of breathing.

9. Good candidates for PEEP have clinically significant hypoxemia that is refractory to inspired oxygen, diffuse acute pulmonary disease, poorly compliant respiratory system, tendency for atelectasis, acute cardiogenic edema with increased left ventricular afterload, audible dependent rales during tidal breathing, or severe airflow obstruction with tidal flow limitation. Virtually all intubated patients are candidates for PEEP of 3 to 5 cm H$_2$O to help offset the lung-compressing effects of recumbency.

10. Choosing the optimum level of PEEP is empirically determined by the response of multiple gas exchange, mechanics, and hemodynamic variables during a well-monitored PEEP trial. A stepwise decremental process that follows a recruiting maneuver is a logical approach to PEEP selection.

11. Auto-PEEP can dramatically increase the work of breathing and provoke patient-ventilator dyssynchrony. In many patients with flow limitation during tidal breathing, these problems can be addressed by adding an appropriate level of PEEP that minimizes end-expiratory airflow without raising the peak alveolar pressure significantly.
GENERAL CONCEPTS AND DEFINITIONS

Hypoxemia resulting from alveolar collapse or edema often responds to alveolar recruitment, avoidance of mechanical instability, and maintenance of functional lung units with positive end-expiratory airway pressure (PEEP). Adding PEEP helps keep lung units patent but may further distend those that are already open. When PEEP maintains recruited lung volume, it not only improves arterial oxygenation but also may reduce the elastic work of expanding the lung or improve the distribution of ventilation. Conversely, PEEP added to an already "open" lung without compensatory recruitment tends to create dead space, increase mechanical lung strain and possibly worsen oxygen exchange. Maintaining adequate end-expiratory lung volume helps prevent ventilator-induced lung injury (VILI) during the initial stages of the acute respiratory distress syndrome (ARDS), reduces alveolar edema, and is useful in avoiding complications after thoracic and upper abdominal surgery.

This chapter focuses primarily on the use of PEEP in hypoxemic respiratory failure; this objective is quite distinct from that of adding PEEP to reduce the work of breathing and improve breath triggering (without increasing the lung volume) during flow-limiting airflow obstruction. The latter important topic is addressed elsewhere (see Chapter 25).

Positive end-expiratory alveolar pressure, or “total PEEP” (PEEP$_T$), is the sum of PEEP applied intentionally at the airway opening (PEEP or “extrinsic” PEEP) and auto (“occult,” “inadvertent,” or “intrinsic”) PEEP (PEEP$_i$). The expressions “assisted ventilation with PEEP” and “continuous positive pressure breathing” both refer to mechanically delivered tidal breaths with positive pressure maintained at end-expiration (Fig. 9-1). By convention, when airway pressure is positive at the end of expiration during assisted mechanical ventilation, the acronym is “PEEP.” During spontaneous breathing cycles, it is called “continuous positive airway pressure,” or “CPAP.” In practice, CPAP has come to imply that the patient provides some or all of ventilating power while PEEP suggests that the ventilator carries most or all of the breathing workload. The terms are often interchanged, however, as they will be in this chapter—the key principles underlying PEEP and CPAP are identical. When two levels of PEEP are alternated, with spontaneous breaths occurring during each phase, the mode is termed “biphasic positive airway pressure” or “BIPAP.” (In this context, the term BIPAP must not be confused with “bilevel,” commercially known as BiPAP, which has been applied to a combination of pressure support and CPAP intended for noninvasive ventilation applied via mask [see Chapter 7].) If the lower level of BIPAP is maintained only transiently (e.g., within the span of a single exhalation), the mode is referred to as “airway pressure release, APRV.” Several of these PEEP variants are discussed elsewhere in this volume (see Chapters 7 and 10). The discussion here will focus on single levels of end-expiratory alveolar pressure.
FIGURE 9-1. Airway pressure waveforms during spontaneous breathing and machine assistance. During a fully spontaneous breath (left), or during those aided by pressure support, “CPAP” is the appropriate term. When positive pressure is the primary energy source used for tidal inflation as in assist control (right), the positive end-expiratory pressure is referred to as “PEEP.”

PATHOPHYSIOLOGY

Actions of PEEP in Acute Hypoxemic Respiratory Failure

The normal lung requires no PEEP to maintain full recruitment—periodic sighs are sufficient to prevent or reverse the widespread alveolar collapse. When the chest cavity is reduced in size (e.g., after abdominal surgery), the lung is edematous or infiltrated (e.g., pulmonary edema), or the alveoli are inherently unstable (surfactant depletion, ARDS), small airways are predisposed to closure, particularly in gravitationally dependent regions. Collapsed units open over a spectrum of transalveolar pressures, determined by airway pressure and the local tissue and pleural pressures that surround them. Even in ARDS, most (but not all) collapsed units recruit at alveolar pressures lower than 25 cm H₂O. Once opened, a lower airspace pressure (PEEP or CPAP) must be sustained in unstable units to prevent their reclosure. The utility of PEEP in improving arterial oxygenation, in minimizing VILI, and perhaps in preventing pneumonia stems primarily from its ability to impede the recollapse of edematous or compressed alveoli recruited by higher pressures (Table 9-1).

Table 9-1. Benefits and Problems of Positive End-Expiratory Airway Pressure

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Problems</th>
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<tbody>
<tr>
<td>Improves oxygenation</td>
<td>May predispose to over distention and barotrauma</td>
</tr>
<tr>
<td>Reduces work of breathing</td>
<td>Impedes preload and right ventricular ejection</td>
</tr>
<tr>
<td>Improves lung compliance</td>
<td>Reduces cerebral perfusion</td>
</tr>
</tbody>
</table>
Aids the left ventricle
Splints the chest wall
Mobilizes distal secretions
Impairs pumping efficiency of respiratory muscles
Increases dead space
Confounds monitoring

FIGURE 9-2. Effect of PEEP on number of junctional lung units and on their associated tissue stress. The relative number of junctional collapsed units at high risk for injury declines as PEEP increases, as shown by the declining width of the stepped blocks. The unchanging block heights reflect the constant tidal driving pressure. The dashed black line indicates the pressure threshold for tissue injury. At the same time, the stresses on these tissues at the junctions of closed and open lung units progressively intensifies, as shown by the deepening shade of red coloration.

PEEP applied to lung units that are already open increases alveolar dimensions, resting lung volumes, and pleural pressures. In the setting of ARDS, this unnecessary increase of pressure is accompanied by augmented global strain, greater inflation energy requirements, and higher stresses that risk VILI for high-risk junctional units at the interface between open and closed units (Fig. 9-2). Distention unaccompanied by recruitment also tends to redirect blood flow, increase vena caval resistance to venous return, create ventilatory dead space, and redistribute alveolar liquid to the interstitial space. In a heterogeneous lung with unstable alveoli and a range of transalveolar pressures, alveolar opening may occur in different regions throughout inspiration, particularly when PEEP is low and tidal volume ($V_T$) is high. When PEEP is added to an unchanging tidal volume, collapsed lung units are opened by the relatively high alveolar pressures (amplified by interdependence) that occur near the end of the inspiratory cycle; PEEP prevents their
reclosure during expiration. Oxygenation may benefit by at least two other mechanisms. When PEEP reduces cardiac output, blood flow through shunt regions may also decline, reducing venous admixture. Perhaps more importantly, as PEEP improves the distribution of alveolar liquid and translocates fluid from alveolar to interstitial spaces, it lowers diffusion distances for oxygen exchange. In the presence of alveolar edema, PEEP may prevent airway flooding by expanding the alveolar reservoir and encouraging fluid migration to the interstitium. By inhibiting distribution of proteinaceous and mediator-laden biofluids via the airway network, both actions may play an important role in the prevention of injury propagation, as described in Chapter 8. (Conversely, abrupt removal of PEEP may precipitate translocation of alveolar liquid into the airways, impeding airflow and occasionally generating froth.) Most available data indicate that PEEP redistributes but does not decrease the total lung water.

**Interaction of PEEP and Tidal Volume**

Recruitment of lung volume is a joint function of PEEP and the opening pressures generated in response to tidal volume. Airways open at higher volumes and transstructural pressures than those at which they close (see “Recruiting Maneuvers”). Therefore, to achieve the same effect on oxygenation and compliance, higher values of PEEP may be needed when tidal volumes are smaller (Fig. 9-3) (see Chapter 25). Moreover, even if calculated tidal (chord) compliance values are identical, failure to maintain sufficient PEEP may result in tidal opening and closure of dependent lung units, a process that may produce stress focusing and shearing stresses that predispose to damage of delicate lung tissues. Some experimental evidence suggests that the *variation* in tidal volume normally observed during health (“biologically variable” or “noisy” ventilation) serves an important recruiting function. The same minute ventilation achieved after lung injury with monotonous tidal volumes is associated with less effective oxygenation than is the identical ventilation accomplished with varying tidal volumes. Any benefit is believed to be due (at least in part) to the avalanches of recruitment that occur when the higher inspiratory pressures are transiently applied.
that the clinical objective is to maximize tidal compliance, there is no single “best PEEP” value relevant to all tidal volumes. Higher values of PEEP are needed to achieve optimal compliance (and least driving pressure) when small tidal volumes are used. PEEP, positive end-expiratory airway pressure.

**Importance of Chest Wall Compliance**

Volume changes resulting from PEEP are shared equally by the lungs and chest wall. Assuming that exhalation occurs passively, the volume resulting from PEEP ($\Delta V$) depends on the compliance of the entire respiratory system, which itself is a function of both lung ($C_L$) and chest wall ($C_W$) compliances:

$$\Delta V = PEEP_t \times C_{rs}$$

$$= PEEP_t \times \left[ \frac{(C_L C_W)}{(C_L + C_W)} \right]$$

As discussed elsewhere (Chapter 5), the pressure distending the lung itself at end-expiration is ($PEEP_T - P_{PL}$), whereas the pressure that distends the passive chest wall is $P_{PL}$ alone. It follows that the volume-expanding and hemodynamic effects of PEEP are influenced by chest wall compliance (Fig. 9-4). A very obese patient or one with a recently operated abdomen or rib cage requires relatively more PEEP to keep the lung adequately recruited, and $P_{PL}$ tends to rise disproportionately with each PEEP increment. Local variations in the compliance of the chest wall help explain the heterogeneity of infiltration and lung expansion in the settings of pulmonary edema acute lung injury.
FIGURE 9-4. Effect of chest wall compliance on lung volume. The effect of positive airway pressure (20 cm H\textsubscript{2}O) on lung volume is influenced by the compliance of the chest wall. In this example, the distending force across the lung is 25 cm H\textsubscript{2}O when the normal chest wall expands during spontaneous breathing, but only 15 cm H\textsubscript{2}O when the poorly compliant chest wall is passively inflated. A patient with a stiff chest wall requires a higher PEEP to achieve the same physiologic effect on the lung.

FIGURE 9-5. Influence of the gravitational gradient of transpulmonary pressure on regional alveolar mechanics. Dependent alveoli at the base of the lung may remain collapsed at airway pressures that threaten to overdistend those in nondependent regions. The contour of the airway pressure-volume curve blends contributions from both populations of units. Regional mechanics are especially heterogeneous in the setting of ARDS. To counterbalance this gradient, modification of regional chest wall compliance (such as occurs during prone positioning) would be needed to improve the uniformity of distention and ventilation. ARDS, acute respiratory distress syndrome.

Regional Effects of PEEP
Pressure varies from site to site within the pleural space. In the supine position, a ventral-to-dorsal gradient (due to both gravity and lung-chest wall shape matching) causes the pleural pressure that surrounds dependent alveoli to be several centimeters H\textsubscript{2}O greater than that in nondependent regions. This difference increases in the setting of acute lung injury. (The gradient of pleural pressure is less steep in the prone position.) Because alveolar distention is a function of transalveolar pressure (airspace minus surrounding pressure), regional alveolar dimensions and propensities to collapse differ, despite a common airway pressure. As progressively higher pressures are applied, individual lung units pop open at some critical opening pressure but collapse abruptly as airway pressure is withdrawn. PEEP that is sufficient to hold alveoli in the uppermost regions patent throughout the tidal cycle may be insufficient to prevent the collapse of gravitationally dependent ones (Fig. 9-5). This gradient of pleural and transalveolar pressures is likely to explain the markedly dependent distribution of computed tomographic (CT) densities evident.
during the initial stages of acute lung injury, as well as the lower “inflection zone” of improving compliance often observed on the inspiratory pressure-volume curve of the respiratory system early in the course of ARDS. PEEP tends to narrow the pleural pressure gradient if recruitment occurs or if alveoli in all regions are open.

**Regional PEEP and the Prone Position**

Prone positioning buttresses and therefore effectively stiffens the ventral chest wall. Better shape matching between the lung and chest wall also occurs during repositioning. Consequently, the prone position alters the distribution of the lung volume, reducing the gradients of alveolar dimensions and pleural pressure that correspond to a given airway pressure. Distribution of perfusion remains little affected despite better expansion in dorsal regions (Fig. 9-6). Therefore, the distribution of tidal ventilation becomes more homogeneous when prone, and ventilation-perfusion matching and arterial oxygenation tend to improve. Although the distribution of volume is altered dramatically, total lung volume at end-expiration (FRC) increases only modestly or remains unchanged by the turning process.

**Active Expiration**

If exhalation occurs passively (as it does during quiet, unstressed breathing), PEEP achieves its desired effect—of increasing lung volume and the number of open air channels. However, if the resulting lung expansion proves uncomfortable or compromises respiratory muscle efficiency, spontaneously breathing patients may actively oppose PEEP in attempting to limit the volume increase. Active expiration to a volume lower than the equilibrium position that corresponds to the PEEP applied to the passive patient stores potential energy. In this way, PEEP or CPAP may provide a mechanism by which the dyspneic patient can use the expiratory muscles to share the workload otherwise borne entirely by inspiratory muscles. As the expiratory muscles relax, the outward recoil of the chest wall then provides an inspiratory boost (Fig. 9-7). The expiratory muscles are activated normally during vigorous exercise, hyperpnea, and impeded expiration. Opposition to PEEP occurring in a hypoxemic patient may simultaneously attenuate volume recruitment, especially in the peridiaphragmatic zones. By silencing the expiratory muscles, sedation or paralysis restores the volume-recruiting effect of PEEP and can markedly improve oxygenation. In addition, reduced oxygen consumption because of less respiratory effort and agitation may help improve central venous PO$_2$, while the ventilator assumes the task of powering ventilation.

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**FIGURE 9-6. Lung geometry in supine and prone positions.** In the supine position, dorsal regions of the lung (purple) are subjected to higher pleural (and lower transpulmonary) pressures than they are in the
prone position, and oxygen exchange may be compromised. These dorsal regions tend to expand disproportionately in the prone position, whereas sternal regions are only modestly compressed. Perfusion tends to be little affected, giving the lung the equivalent of higher regional PEEP and, when recruitment accompanies expansion, better gas exchange. The prone position has an unpredictable but usually modest effect on the overall resting lung volume. FRC, functional residual capacity.

**FIGURE 9-7. The work-sharing concept.** Expiratory muscles may force the lung below the equilibrium volume appropriate to the applied level of PEEP (in this case, 5 cm H\(_2\)O). This compression reduces FRC and tends to both cause basilar atelectasis and impair oxygenation. Squeezing against PEEP, however, stores potential energy for release in early inspiration, thereby sharing the ventilatory workload of the inspiratory muscles.

**Time Course of PEEP Effect on Gas Exchange**
Although lung recruitment after a step change of PEEP is usually nearly complete within five to ten breaths, the time course is quite variable; several hours may be required to realize the full effect of a given PEEP increment. On the other hand, desaturation usually occurs quite abruptly upon PEEP withdrawal.

**PEEP and Mean Airway Pressure**
Mean alveolar pressure and mean airway pressure, its easily measured analog during passive inflation, are discussed at length elsewhere in this text (see Chapters 5 and 24). It is worth noting here, however, that although mean alveolar pressure can be raised in a variety of ways, PEEP has the most predictable effect on oxygenation, combating end-expiratory lung unit collapse as it raises both mean airway and mean alveolar pressures by the amount of the PEEP applied. Just as PEEP\(_T\) determines the end-expiratory alveolar dimension, in a passive patient the mean airway pressure determines the average or mean alveolar volume. Most cardiovascular effects of PEEP are due to mean alveolar pressure, mediated via its effects on mean intrapleural and right atrial pressures, as well as on RV afterload. Apart from its effect on mean airway pressure, PEEP\(_T\) maintains collapsible alveoli recruited throughout the tidal breath; therefore, it is instrumental in improving oxygen exchange and avoiding VILI. (In fact, it has been argued that raising mean airway pressure by extending inspiratory time while holding PEEP\(_T\) constant may not help markedly to
improve the arterial oxygen delivery.)

ADVERSE EFFECTS OF PEEP

Cardiovascular Impairment

PEEP and Venous Return

At the end of passive exhalation, pressure within the central airway approximates alveolar pressure, provided that expiratory flow has stopped (see “auto-PEEP effect”). Under these quasi-static conditions, an increment of pressure applied to the airway (PEEP) distributes across the lung and chest wall according to the formula:

\[
\Delta P_{PL} = \text{PEEP} \times \left[ \frac{C_t}{(C_t + C_W)} \right]
\]

where \(P_{PL}\) and PEEP refer to pleural and airway pressures and \(C_t\) and \(C_W\) denote the dynamic compliances of the lung and chest wall, respectively. In healthy individuals, the lungs and passive chest wall have similar compliance characteristics in the tidal range near FRC; therefore, approximately one half of the applied PEEP transmits to the pleural space. With abnormally stiff lungs, less is transmitted (typically, one fifth to one third). With compliant lungs and a stiff chest wall (e.g., in a patient with emphysema, obesity, or massive ascites), the pleural pressure increment is a higher than normal fraction of the applied PEEP (Fig. 9-4). Because pressures similar to \(P_{PL}\) surround the heart and great vessels, PEEP reduces venous return but tends to raise all intrathoracic intra-vascular pressures. Such pressure changes complicate the interpretation of central venous pressure (CVP) and pulmonary artery occlusion (wedge) pressure.

Depression of cardiac output is seen rarely during the application of modest levels of CPAP to a spontaneously breathing patient. Compared with passive inflation, the magnitude of the CPAP-induced rise of mean intrapleural pressure is routinely small. Moreover, inspiratory descent of the diaphragm (and expiratory effort, if any) boosts intra-abdominal (and therefore upstream) venous pressures relative to their intrathoracic values, improving venous return.

Extreme lung expansion may compress the inferior vena cava (IVC) at the thoracic inlet, increasing the resistance to venous return (Fig. 9-8). Lung expansion lifts the supine heart and depresses the diaphragm, thereby stretching the IVC, which is tethered at the diaphragm, pericardium, and retroperitoneum. Whether caval compression is important when the lungs are stiff (and volume changes are small, as they tend to be in ARDS) is an unanswered question.

PEEP and Ventricular Afterload

Although PEEP may raise pulmonary vascular resistance, this effect is relatively unimportant when the lung retains its normal capacity to accept gas. Right ventricular performance remains little affected unless pulmonary capillary reserve is exhausted, the right ventricle is already failing, or peak and mean alveolar pressures rise to quite elevated levels. It is worth noting that only a small fraction of the lung may remain accessible to gas in severe ARDS—typically one third or less of the normal amount. In patients without pleural effusion, the sum of gas, tissue, and liquid in the injured lung is approximately normal and equals the total injured volume occupied by the chest wall that surrounds it. In this setting, therefore, the cardiovascular effects of alveolar overdistention, pulmonary hypertension, right ventricular afterload, and left ventricular filling restriction associated with right ventricular dilation may predominate over those caused by the very modest increases of pleural pressure due to PEEP (Fig. 9-8). Even in less compromised lungs, high levels of PEEP can increase right ventricular (RV) afterload and distention sufficiently to reduce left ventricular compliance by ventricular
interdependence.

FIGURE 9-8. Effects of PEEP on cardiovascular function. As PEEP holds the lungs distended, increased juxtacardiac pressure tends to compress the heart and great vessels, impeding venous inflow to the thorax while raising intracavitary and intravascular pressures. In the setting of severe ARDS, pulmonary vascular compression resulting from alveolar overdistention may increase right ventricular afterload and contribute to cor pulmonale and functionally reduced left ventricular compliance (pictured). PEEP may also narrow the inferior vena cava at the inlet to the thorax, thereby increasing the resistance to venous return as well.

Left ventricular afterload is decreased by raised intrapleural pressure because the systolic myocardial tension that must be developed to achieve any specified systemic arterial pressure is diminished by the external compression that results from augmented pleural pressure. Although such afterload changes are likely to be of little significance during passive inflation, their importance rises when vigorous inspiratory efforts are made. Applying CPAP to patients with pulmonary edema promotes cardiovascular stability, not only by decreasing central vascular volume and improving arterial oxygenation and the work of breathing but also by helping to silence the inspiratory effort, thereby raising intrapleural pressure and reducing afterload. High levels of PEEP have been suggested to cause myocardial dysfunction directly, but such effects, if present at all, are minor.

Compensation for PEEP-induced reductions in cardiac output may be accomplished by increasing heart rate (a compensatory response thought to be blunted by PEEP), raising venous tone, and by sufficient intravascular fluid to raise the pressure driving venous return. These counterbalancing effects are maximized within hours to days. Cardiac output usually remains stable when moderate levels of PEEP are used in normovolemic patients with good cardiovascular reflexes and myocardial reserves. Repletion of intravascular volume, guided by the PEEP-adjusted central venous or wedge pressures, should be the primary treatment for depressed cardiac output resulting from PEEP. When adequate intravascular volume is ensured, vasopressors also may be added to improve the driving pressure for venous return.

Barotrauma
Barotrauma during mechanical ventilation is discussed at length elsewhere in this volume (see Chapter 8). The extent to which PEEP contributes to the tendency for pneumothorax and other forms of extra-alveolar gas accumulation is unclear. When tidal
volume remains unchanged, its primary effects may be mediated by increasing peak and mean alveolar pressures. If peak pressure is controlled, PEEP may contribute negligibly to the risk of alveolar rupture. In fact, when high tidal pressures are generated in the early stages of ARDS, PEEP may be instrumental in reducing shear stresses and avoiding ventilator-induced lung edema. It stands to reason that PEEP might accentuate the risk of rupturing alveoli that are weakened by disease if both peak and driving pressures are allowed to rise. Once ruptured, a PEEP-induced increase in mean alveolar pressure could promote additional gas leakage. These pressures are reduced effectively by lowering the tidal volume and driving pressure ($P_{plat} - PEEP = \frac{V_T}{C}$) as end-expiratory pressure is raised. A lower tidal volume with increased PEEP often results in hypercapnia, which can be either accepted (permissive hypercapnia) or offset by increasing the ventilator’s cycling frequency.

**Reduced Oxygen Delivery**

Although it usually aids tissue oxygenation, PEEP may adversely affect oxygen delivery via four primary mechanisms: (1) decreased cardiac output, (2) increased venous admixture, (3) flow diversion to shunt units, and (4) increased intracardiac or non-capillary shunt. When the adequacy of tissue oxygen delivery is in question, it is mandatory to follow cardiac output as well as $SaO_2$ during manipulations of PEEP, supplemented, when feasible, by determinations of central venous or mixed venous saturation, arteriovenous oxygen content difference $\Delta(a - v)O_2$, or other indications of tissue $O_2$ sufficiency.

PEEP may adversely alter the distribution of pulmonary blood flow, especially in patients with highly regional or asymmetrical lung disease. Positive transpulmonary pressure has its greatest distending effect on compliant alveoli. Therefore, as PEEP is raised to high levels, resistance to blood flow through compliant lung units increases disproportionately, redirecting the blood flow toward stiffer, and often more diseased, areas. At usual levels of PEEP, any such diversion usually does not outweigh the benefits of alveolar recruitment and hypoxic vasoconstriction. PEEP may reduce PaO$_2$ by this mechanism in certain patients with highly regionalized disease that produces poorly recruitable (but perfused) lung units (e.g., lobar pneumonia). In a similar fashion, PEEP can increase the shunt flow in a patient with intrapulmonary or intracardiac right-to-left vascular communications. Pulmonary arteriovenous malformations, atrial septal defects, and the pulmonary shunt vessels of cirrhosis may receive a larger percentage of flow as PEEP raises pulmonary vascular resistance and right heart filling pressure.

**Impaired Vital Organ Perfusion**

**Cerebral Perfusion**

PEEP increases jugular and intracranial pressures (ICP) by raising CVP. Predictably, these increments are less when the lungs are stiff or heavily infiltrated and transmit less pressure to the pleural space. Lower arterial blood pressure (BP) or raised ICP can reduce cerebral perfusion pressure (CPP): $CPP = BP - ICP$. However, in the setting of intracranial hypertension, PEEP-related arterial hypotension presents a considerably greater risk for precipitating cerebral dysfunction than do elevations of central venous pressure. (When ICP exceeds CVP, increases in CVP caused by PEEP do not transmit fully to the cerebral veins.) Abrupt application of PEEP can raise ICP and could help precipitate herniation in patients with intracranial mass lesions or seriously elevated ICP. (If CO$_2$ clearance is impaired by dead space formation, a rising PaCO$_2$ also can contribute to intracranial hypertension.) Abrupt withdrawal of PEEP can cause a surge in venous return, transiently boosting BP and ICP. Despite its potential dangers, PEEP generally can be used safely if high levels are avoided and cardiac filling pressure is adequate and if PEEP is applied and withdrawn in small steps.

**Hepatic and Renal Perfusion**
PEEP-associated reductions of cardiac output, coupled with elevation of CVP, may compromise hepatic perfusion or venous drainage. As with right heart failure, the resulting passive hepatic congestion can mildly elevate bilirubin and hepatic enzymes. PEEP also has been reported to interfere with renal function, even when cardiac output is well preserved. Although a variety of mechanisms (reflex, humoral) have been proposed, none has been generally accepted. If PEEP contributes to excessive intraabdominal pressure (e.g., after extensive abdominal surgery), prerenal oliguria can result.

Impaired CO₂ Elimination

When alveolar recruitment is marginal or nearly maximized (PEEP₁ substantially exceeding P_{flex}), PEEP impairs CO₂ elimination by overdistending patent and well-ventilated lung units, increasing their vascular resistance, and creating high ventilation/perfusion ([V with dot above]/[Q with dot above]) units and wasted ventilation (dead space) (Fig. 9-9). Total pulmonary blood flow also may fall if venous return is seriously impeded. Such changes tend to expand the physiologic dead space, increasing the ventilation requirement and encouraging CO₂ retention in patients with marginal ventilatory reserves. Fortunately, these effects usually are modest. Alveolar overdistention may be signaled by a widened difference between arterial and mixed expired or end-expiratory values of PCO₂ determined by exhaled capnography.

Alterations in the Work of Breathing

Although modern ventilator circuits maintain airway pressure nearly constant throughout the spontaneous breathing cycle, older ones may impose substantial airflow resistance, particularly when PEEP is used. PEEP itself may either increase or decrease the work of breathing (W_B). Alveolar recruitment tends to reduce the W_B, but overdistention sometimes proves detrimental on two counts. First, lung compliance may worsen as additional volume is forced into a fully recruited lung, increasing lung tension and elastic workload. Second, chest distention limits the ability of the inspiratory muscles to perform work by placing them on a disadvantageous portion of their length-tension relationship and altering muscle geometry. When the expiratory muscles oppose volume recruitment, the total (inspiratory plus expiratory) W_B tends to increase. As already discussed, however, PEEP may redistribute the ventilation workload by facilitating transfer of inspiratory effort to the expiratory muscles.
Fig. 9-9. Relationship of PEEP to alveolar recruitment, arterial oxygenation, oxygen delivery, and physiologic dead space. Potential for alveolar recruitment is nearly completed at high levels of PEEP, whereas dead space fraction and cardiovascular compromise (as reflected in declining $O_2$ delivery) tend to progressively increase as PEEP rises further.

**CLINICAL USE OF PEEP**

**Good Candidates for Higher PEEP**

Based on the foregoing discussion, good candidates for a trial of raising PEEP are those who have (1) acute hypoxemia despite an elevated $FiO_2$, especially in the early phase of ARDS support, (2) diffuse acute pulmonary infiltrates, (3) a poorly compliant lung or chest wall (e.g., massive obesity), (4) adequate cardiac reserve with normal to increased intravascular volume, (5) a tendency for atelectasis (e.g., after upper abdominal surgery), (6) acute cardiogenic or noncardiogenic pulmonary edema, (7) increased left ventricular afterload, (8) a pressure-volume relationship characterized by a lower inflection zone of rapidly improving compliance, and (9) severe airflow obstruction with flow limitation during tidal breathing, characterized by increased work of breathing and inconsistency in triggering the ventilator. In the nonintubated patient, PEEP may help compensate for reversible upper airway obstruction, such as that encountered during obstructive sleep apnea, certain variants of asthma, and postextubation laryngeal or glottic edema.
Poor Candidates for Higher PEEP
Although there is a good rationale for using at least 3 to 5 cm H\(_2\)O PEEP or CPAP for almost every intubated patient (see the following section), poor candidates for higher levels have (1) unilateral or localized lung disease, (2) cardiovascular compromise or hypotension resulting from intravascular volume deficits or right ventricular dysfunction, (3) severe intracranial disease or hypertension, or (4) pulmonary hyperinflation without tidal flow limitation. Whatever the relative contraindications, a cautious and well-monitored trial of PEEP should not be withheld from apparently poor candidates with refractory hypoxemia.

Physiologic PEEP
Considerable volume loss occurs in moving from the upright to the supine horizontal position in all but severely obstructed or massively obese patients (Fig. 9-10). (A normal young person loses about 1 L of lung volume in this transition.) Positional volume losses occur disproportionately in juxtadiaphragmatic regions. Because the compliance of the normal respiratory system approximates 80 to 100 mL/cm H\(_2\)O, approximately 10 cm H\(_2\)O PEEP would theoretically be needed in recumbency to restore an end-expiratory lung volume equivalent to that of the upright position. Other positional changes are also important to consider. Side-to-side turning increases the volume of the upper lung as the shifting abdominal contents alter the regional chest wall compliance. Overall, end-expiratory volume may be modestly higher in the lateral decubitus position than in the supine position. The prone position helps dramatically for some patients with diffuse lung injury, usually because it causes a regionally intense distending pressure in the dorsal and juxtadiaphragmatic regions that most need it, not primarily because proning increases overall lung volume. PEEP may reduce the work of breathing and, in the earliest stage of ARDS, may also help protect against VILI, lung infection, and dissemination of lung bacteria and the products of inflammation to the systemic circulation—especially when coupled to reduced driving pressure.
FIGURE 9-10. Influence of lateral decubitus and supine postures on resting lung volume. In a normal subject, a volume loss of approximately 900 mL (equivalent to 5 to 10 cm H₂O PEEP) occurs in the transition from the sitting to the supine horizontal position. Somewhat less volume is lost in assuming the lateral decubitus position. (Modified from Marini JJ, et al. Am Rev Respir Dis. 1984;129:101-105, with permission.)

Choosing the Appropriate Level of PEEP
As end-expiratory pressure is raised, the effect is neither smooth nor predictable. Some patients show little response until very high levels are reached, at which point oxygen exchange may improve remarkably; others respond adequately at 5 cm H₂O (or even less if upright). As a rule, diffuse infiltrates are most responsive. Highly regionalized diseases, as demonstrated on CT scans, tend to be relatively refractory to PEEP. Because the beneficial effect of PEEP on transpulmonary oxygen transfer parallels recruitment of collapsed lung units, PEEP responsiveness tends to be greatest during the earliest phase of acute lung injury, when edema and atelectasis are most prevalent. Low levels of PEEP may be insufficient to maintain alveolar patency, especially when used in conjunction with modest tidal volumes. As more PEEP is added to a small tidal volume, peak inflation pressures rise and collapsed alveoli reinflate. As a consequence, venous admixture falls, and improving arterial oxygenation accompanies improving C₅₅. The application of PEEP to the problem of ARDS management is discussed more thoroughly in Chapter 24.

Alternatives for Choosing “Optimal PEEP”
The effects of PEEP on gas exchange may vary with tidal volume, and the maximal response to a given PEEP increment—although generally rapid—may require 1 hour or more to establish. As discussed earlier and in Chapter 8, adequate PEEP to ensure ample and sustained recruitment of functional lung units may be of fundamental importance in improving gas exchange while averting VILI, and yet excessive PEEP risks overstretching open tissue. There is no consensus regarding what constitutes an optimal level of PEEP; however, oxygen saturation, oxygen delivery, venous admixture, lung compliance, inspiratory and expiratory pressure-volume curves, minimal dead space, and volume recruitment all have been proposed to guide its selection (Table 9-2). Recent data suggest that for most patients, further “recruitability” potential is usually very modest, once PEEP exceeds 12 to 15 cm H₂O PEEP (see Fig. 8-12). Moreover, because mechanics and gas exchange efficiency are rather tightly linked, the PEEP values selected by these different optimal PEEP strategies often—but not invariably—coincide. This is not to say that initial opening of compromised lung units does not require high pressure—it often does. Best results for lung unit recruitment tend to be obtained during the stepwise release of a high-pressure recruiting maneuver while ventilating with the small tidal volume to be used during support, a process known as decremental PEEP selection after a recruiting maneuver (Fig. 9-11).

Table 9-2. Targeted Variables for “Optimal Positive End-Expiratory Airway Pressure”

<table>
<thead>
<tr>
<th>Variable</th>
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<tbody>
<tr>
<td>O₂ saturation (arterial or mixed venous)</td>
</tr>
<tr>
<td>O₂ delivery</td>
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<tr>
<td>Minimal venous admixture</td>
</tr>
<tr>
<td>Minimized dead space</td>
</tr>
<tr>
<td>Best tidal compliance</td>
</tr>
<tr>
<td>Least driving pressure for tidal volume used</td>
</tr>
<tr>
<td>Volume recruitment</td>
</tr>
<tr>
<td>Above lower inflection zone of inflation P-V curve</td>
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</table>
Transpulmonary pressure at end-expiration

**FIGURE 9-11. Stepwise “decremental” selection of best PEEP after a recruiting maneuver.** Because PEEP cannot keep open what has never first been opened, an attempt is made to safely recruit the lung (which may require high airway pressures) without hemodynamic compromise. PEEP steps on the down side of the “staircase” are smaller and are made more slowly than are those made during the increasing PEEP and recruiting maneuver phases. In this example, recruitment is achieved by using pressure-controlled ventilation and very high PEEP. Best PEEP is found on the deflation limb, monitoring compliance, oxygenation, or end-expiratory transpulmonary pressure.

A “traditional” method for conducting a PEEP trial is outlined in **Table 9-3**. It should be understood that, despite its effectiveness in improving $O_2$ saturation or preventing lung unit collapse, adding PEEP may prove detrimental if it unnecessarily increases tissue stresses, generates significant dead space, or impairs $O_2$ delivery by reducing cardiac output. Most physicians choose the minimal level of PEEP required to sustain an acceptable arterial oxygen saturation (generally $>90\%$) at a tolerable $FiO_2$ (ideally $<0.7$). A close watch must be kept on peak, mean, and driving airway pressures; a marginal boost in $PaO_2$ or in $O_2$ delivery may not be worth an increased risk of VILI or lung rupture.

| Table 9-3. One “Traditional” Method for Selecting Positive End-Expiratory Airway Pressure |
| Define |
Least tolerated PaO$_2$ or SaO$_2$
Maximum acceptable FiO$_2$
Least tolerated cardiac output or blood pressure
Maximum tolerated peak or plateau airway pressure
Desired tidal volume

**Follow**
- PaO$_2$
- SaO$_2$
- Cardiac output (if available)
- Arterial blood pressure
- Plateau pressure
- Tidal compliance or driving pressure (volume control)
- Tidal volume (pressure control)

**Sequence in early ARDS** (volume-cycled ventilation)
- Begin with PEEP approx. 8 cm H$_2$O
- Increase PEEP in steps of 2-3 cm H$_2$O to tolerance or desired effect
- Adjust $V_T$ if peak pressure rises too high
- Consider raising targeted plateau pressure
- Consider adding recruiting breaths if $V_T < 6$ mL/kg

An optimal PEEP can be selected without the benefit of wedge pressure or SvO$_2$ measurements by raising PEEP during passive ventilation while monitoring “total thoracic compliance.” Advocates of this time-honored method note that the level of PEEP that maximizes tidal (chord) compliance (and for a given tidal volume minimizes the driving pressure), tends to coincide with the greatest oxygen delivery and lowest alveolar dead space fraction. For some patients, the peak of the compliance curve is not sharp; in others who are not fluid primed, total thoracic compliance may continue to improve as PEEP is raised to levels that induce hypotension. Two other optimization methods can be considered variants of this optimal recruitment model. The first compares arterial and end-tidal CO$_2$ tensions. This difference narrows as recruitment outpaces dead space formation caused by regional overdistention and widens again as overdistention begins to predominate. Although theoretically appealing, this “dead space minimization” method is time consuming and unreliable in practice, as CO$_2$ stores are large, CO$_2$ exchange kinetics are slow, and vascular shunt flow contributes to the dead space fraction (see Fig. 5-5). The second variation of the optimized recruitment model uses the static airway pressure-volume curve as a guide to identify the point of nearly full lung recruitment. Until recently, the lower inflection “point” of the inflation PV curve was thought to identify the end of recruitment, and, therefore, a slightly higher pressure identified a suitable PEEP to target. CT imaging has confirmed, however, that this interpretation is misleadingly simplistic. Recruitment of refractory lung units continues until pressures are reached that approach the upper inflection zone. The contours of the *inspiratory* PV curve reflect the simultaneous interplay among lung units that are recruited and overdistended, and the proportions of each vary as airway pressure rises. Factors such as volume-related chest wall compliance changes, gas trapping, and shifts of airway liquids further complicate the analysis. The deflation limb of the PV relationship, that portion of the loop relevant to expiratory events such as relaxation to PEEP, is left-shifted on the pressure axis with respect to its inspiratory counterpart. Theoretically, changes in tidal compliance caused by closure should be more informative regarding PEEP selection than inspiratory (opening) contours. (This is the core principle of the decremental approach to PEEP)
selection.) Yet, this deflation limb of the PV loop also reflects the interplay between relaxation of regional overdistention and development of lung unit collapse, and like its inspiratory counterpart, it is influenced by factors unrelated to airway closure. Although the decremental approach makes solid physiologic sense, at least one well-conducted clinical trial suggested that decremental PEEP setting held little advantage over less complicated methods (e.g., a standardized and published PEEP-FiO2 Table of the ARDS Network).

As esophageal pressure measurement by balloon catheter has become more widely practiced to assess pleural pressure (see Chapter 5), some practitioners have reasoned that the calculated transalveolar pressure at end expiration should turn positive at the minimum PEEP associated with regional aeration and reversal of collapse (see below). Selecting PEEP to be 2 to 5 cm H$_2$O greater than this “transition” value (to offset what might be an artifact due to the weight of

the mediastinum that overlies the balloon in the supine position) usually results in best PEEP values higher than reached by other mechanics-based methods, especially in patients with morbid obesity (with or without ARDS). Which of these methods for setting PEEP is most appropriate remains actively debated.

**Selecting PEEP and Tidal Volume in ARDS**

Certain principles should guide the approach to PEEP and tidal volume selection in patients with acute lung injury. These include the following:

1. Adjust ventilatory parameters empirically, rather than by formula-driven rules; prioritize patient comfort and safety. Although PEEP/FiO$_2$ tables may be convenient, they are imprecise.

2. Assign the prevention of mechanical trauma precedence over maintenance of normocapnia and avoidance of oxygen toxicity. Both recruitability and VILI risk appear greatest very early on during ventilator support and diminish afterward. Because chest walls vary, no exact upper limits for acceptable plateau pressure can be specified.

3. Very high values for FiO$_2$ risk absorption atelectasis as well as oxygen toxicity. Therefore, FiO$_2$ should be held to less than 0.7 whenever possible.

4. Consider the impact of chest wall stiffness (including abdominal contents) on transpulmonary pressure and gas exchange efficiency. In concerning cases, determine the abdominal (bladder) and/or esophageal pressures.

5. Monitor hemodynamics as well as mechanics and gas exchange when regulating ventilatory therapy. A surrogate for measuring hemodynamics directly may be to monitor the central venous oxygen saturation. A value greater than 70% and a difference of 25% or less between arterial and central venous saturations are usually associated with an adequate cardiac index (>2.5 L/m$^2$/min).

6. In severe cases, attempt to minimize ventilatory demands and thereby reduce airway pressures, high rates of gas flow, and cardiac output requirements.

7. Unless otherwise contraindicated, prone positioning should be considered when dangerously high values for ventilatory pressure, PEEP, and FiO$_2$ are needed to maintain adequate supine arterial oxygen tension.

**Targets for Ventilation and Oxygenation**

As a general rule, the desired goal is to use the least PEEP and tidal volume necessary to achieve acceptable gas exchange while minimizing tidal collapse and reopening of unstable lung units. Knowing that moderate hypercapnia is generally well tolerated, therapeutic targeting priorities are directed toward lung protection and maintenance of appropriate hemodynamics and oxygen delivery.
Utility of Recruiting Maneuvers and Auscultation in PEEP/Tidal Volume Selection

All patients should be assessed for severity of disease and for recruitment potential. Recruiting maneuvers help characterize PEEP responsiveness, determine the relative status of intravascular filling and response to altered cardiac loading conditions, and set the PEEP/tidal volume combination. After deficits of intravascular volume have been addressed and hemodynamics have been optimized, recruitment potential is gauged by applying “high-level” pressure control ventilation: PEEP of 15 to 30 cm H\textsubscript{2}O, driving pressure of 15 to 20 cm H\textsubscript{2}O, and plateau pressure of approximately 50 cm H\textsubscript{2}O for 1 to 2 minutes, as tolerated. Even higher pressures may be appropriate for a patient with a very stiff chest wall—for example, a burn victim with chest wall edema or eschar. Although sustained inflation with high pressure has been traditionally used, widely employed, and selected for most reported research, it is no more effective and tends to be less well tolerated hemodynamically than a recruiting method based on pressure-controlled ventilation that achieves lower average pressure but similar peak pressure during its inspiratory phase.

If oxygenation and lung mechanics do not improve substantially with high-level pressure-controlled ventilation as a recruiting technique, the patient is considered to have low recruiting potential \textit{in that position and at that specific time}. Management goals in the “recruitable” group emphasize the maintenance of adequately high end-expiratory pressure, whereas in poorly recruitable patients, PEEP is maintained as low as feasible—generally in the range of 5 to 10 cm H\textsubscript{2}O. In both groups, end-inspiratory plateau pressure is kept less than 30 cm H\textsubscript{2}O and driving pressure less than 15 cm H\textsubscript{2}O, except when chest wall compliance is very low.

Patients with an extensive recruitable population of lung units respond to increased PEEP and recruiting maneuvers with improved alveolar mechanics and improved gas exchange, reflected both by increased PaO\textsubscript{2} and by better ventilating efficiency, as gauged by a reduced V\textsubscript{E}/PaCO\textsubscript{2}. These salutary changes are accompanied by only marginal effects on hemodynamics, as judged by systemic BP and central venous oxygen saturation.

Inspiratory crackles (rales) audible over the dependent zones of the chest during routine tidal cycles suggest that recruitment and derecruitment are occurring with each breath and indicate that recruitment maneuvers followed by higher levels of end-expiratory pressure may be indicated to silence them. Crackles occurring \textit{late} in inspiration are of particular concern, as they may originate in units opening under relatively high pressures. In gauging response to PEEP, it is important to consider CO\textsubscript{2} exchange as well as oxygenation response. With rare exceptions (e.g., when PEEP-impaired cardiac output causes mixed venous O\textsubscript{2} content to fall), PaO\textsubscript{2} tends to increase when PEEP is applied. However, this oxygenation improvement may be accounted for either by recruitment of lung units or by reduced or redirected blood flow within the injured lung. In the latter circumstance, PaCO\textsubscript{2} may rise simultaneously. When recruitment is the explanation for O\textsubscript{2} improvement, however, CO\textsubscript{2} exchange is not compromised and may even improve, reflecting increased alveolar ventilation.

Similar principles of PEEP titration apply during prone positioning. Perhaps surprisingly, however, it has been shown in several experimental and clinical studies that the PEEP associated with best compliance and least driving pressure is quite similar for the prone and supine positions, despite the stiffening of the chest wall that occurs with the former.

\textit{Initial Preparations Prior to PEEP Selection in ARDS}

1. Decide whether to allow inspiratory efforts, using controlled or nearly controlled ventilation to subdue vigorous respiratory efforts for the most severely involved patients during the early stage of support.
Establish a ventilation baseline. With the patient gently breathing or passive, a reasonable set of initial ventilatory settings (just after intubation) might be FiO₂ 0.8 and PEEP 8 to 10 cm H₂O (depending on the concern regarding hemodynamic tolerance); tidal volume 5 to 8 mL/kg (depending on the inspiratory plateau pressure).

Estimate intravascular volume status initially from arterial BP, respiratory variations of pulmonary and systemic arterial pulse pressure during passive ventilation, CVP, urinary output, and urinary electrolytes.

Confirm adequacy of intravascular volume utilizing echocardiography, results from a volume challenge, and central venous and/or pulmonary artery catheter data (cardiac index, mixed venous O₂ saturation, and occlusion pressure), if available.

Replenish any volume deficits and support the circulation with pressors and inotropes to the extent necessary to safely perform the ventilatory manipulations.

Determine the recruitment potential of the patient by conducting a recruiting maneuver/PEEP trial.

**Determining “Best PEEP”**

As already noted, no consensus yet exists regarding the best method of conducting a PEEP trial in patients with edematous or injured lungs. Whatever the protocol, however, oxygenation response, ventilatory efficiency, alterations of mechanics, and hemodynamic response should be considered together. During the trial, PEEP level should be the only manipulated variable. (Note that although PEEP may be most easily set during passive conditions, its best value may change with effort.) Position, level of sedation, FiO₂, tidal volume or pressure control level, and all other ventilator settings remain at fixed, safe levels. Given that airways open at pressures higher than those that keep them open, a recruiting maneuver should be considered integral to an adjustment aimed at optimizing the PEEP selection (i.e., recruiting maneuver precedes each PEEP increase). PEEP can be either increased incrementally or, preferably, decreased decrementally (Fig. 9-11). Several PEEP levels should be tried, and the previously mentioned variables that are influenced by recruitment, over-distention, risk of VILI, and hemodynamic response should be monitored. During volume-controlled ventilation with the low (5 to 7 mL/kg pbw) to be used in practice, minimizing the driving pressure is an attractive option (Table 9-4).

**Using Esophageal Pressure to set PEEP**

The esophageal balloon catheter is designed to estimate pleural pressure (Pₚₑₛ) at its site of measurement (as described in Chapter 5). The difference between the static airway pressure and Pₚₑₛ tracks with acceptable accuracy the changes in transpulmonary pressure occurring across the lung itself (Pₜₚ = PEEP - Pₚₑₛ). The absolute value of Pₚₑₛ, although not reflecting average pleural pressure, does reflects the plural pressure existing in its local region and perhaps across its entire horizontal plane. When Pₚₑₛ exceeds PEEP, the computed end expiratory transpulmonary pressure becomes negative, theoretically indicating local collapse of the adjacent parenchyma. As recruitment of that tissue occurs, Pₜₚ turns positive, theoretically indicating aeration (recruitment) of those same lung units. The pressure at which that transition from negative to positive Pₜₚ occurs is an optimal PEEP for those alveoli. (When PEEP is set decrementally after a recruiting maneuver, the relevant transition point is from positive to negative end-expiratory Pₜₚ.) The Pₜₚ calculated in this way, incremented by 2 to 4 cm H₂O to allow for reinflation of compressed but potentially recruitable lung units below the plane of the balloon catheter, has been reported helpful for titrating PEEP in ARDS as well as for patients with massive obesity. Such results suggest that whether the dependent parenchyma collapses because of abnormalities of lung or chest wall, such computations
of $P_{tp}$ are of high value. PEEP settings resulting from this approach are generally higher than when using the decremental strategy that monitors airway driving pressure or oxygenation. Whether this esophageal pressure-based technique will be confirmed to hold a reproducible advantage over other methods for selecting PEEP has yet to be determined in definitive fashion.

<table>
<thead>
<tr>
<th>Table 9-4. Finding the “Best Peep” Compromise Decrementally</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Minimize effort and ventilation demand</td>
</tr>
<tr>
<td>• Choose the $V_T$ or driving pressure to be used in practice (e.g., 6 mL/kg or 12 cm H₂O)</td>
</tr>
<tr>
<td>• Use least acceptable FiO₂ to keep SaO₂ approx. 92%</td>
</tr>
<tr>
<td>• Perform a recruiting maneuver using that $V_T$ with escalating PEEP to 50-60 cm H₂O peak pressure (3-5 breaths at each PEEP level)</td>
</tr>
<tr>
<td>• Drop PEEP abruptly from its highest value to 20-25 cm H₂O and then reduce PEEP further in small steps (e.g., 2 cm H₂O every 2-3 min) until:</td>
</tr>
<tr>
<td>o O₂ sat falls or driving pressure begins to rise (volume control)</td>
</tr>
<tr>
<td>o O₂ sat falls or tidal volume declines (pressure control)</td>
</tr>
<tr>
<td>o End-expiratory transpulmonary pressure transitions from positive to negative</td>
</tr>
<tr>
<td>• Rerecruit and drop PEEP to that threshold value plus one step higher</td>
</tr>
</tbody>
</table>

**PEEP Withdrawal**

Clinically unstable patients, that is, those requiring a FiO₂ higher than 0.5 and those with worsening gas exchange may not tolerate PEEP withdrawal. However, after the first few days of supporting ARDS, a time when atelectasis and alveolar edema are less prevalent, it is important to attempt to reduce PEEP to the lowest well-tolerated level while maintaining an acceptable FiO₂. A more upright position may help maintain recruitment (especially of gravitationally dependent tissues) and facilitate PEEP withdrawal. PEEP should be withdrawn cautiously, with oximetry or arterial blood gas monitoring at each step change. A patient who has shown only marginal PEEP response is a possible exception to these guidelines. Abrupt or premature withdrawal of PEEP can cause lung unit collapse with deterioration of gas exchange, which may respond only slowly to the restoration of PEEP if a recruiting maneuver is not performed. Sudden termination of PEEP also risks cardiovascular overload, increases the work of breathing, results in airway flooding with alveolar fluids, and precipitates dangerous increases in ICP.

**“Prophylactic PEEP”**

The routine application of low-level PEEP (e.g., 5 cm H₂O) to the airway of patients who require intubation rests on firm conceptual ground. As noted earlier, lung volume is reduced substantially by recumbency, especially at the lung base (Fig. 9-10). Moreover, PEEP could offset the additional fall in FRC known to occur in the first few
hours to days after thoracic or upper abdominal incisions (a factor contributing to atelectasis and impaired gas exchange). At the present time, there is no convincing proof of benefit or danger from this approach. A PEEP of 8 cm H$_2$O (generally less than $P_{flex}$) has not been shown to protect routinely against the development of ARDS, whatever benefit PEEP might confer on O$_2$ exchange or lung mechanics once ARDS is under way. There is intriguing experimental evidence that PEEP may help in the prevention of propagation of initially localized lung injury (see Chapter 8). PEEP maintenance tends to keep inflammatory biofluids at the periphery of the lung and confined to their sites of origin rather than allowing spread to adjacent sectors (see Chapter 7).

**“Auto-PEEP” Effect**

Patients who trap air above the relaxed volume of the chest maintain positive pressure in the alveoli and small airways at end-exhalation in excess of the value set at the airway opening. This excess pressure, or auto-PEEP (AP), may create dynamic hyperinflation, which raises intrathoracic pressure and during passive breathing often impedes venous return. As discussed in greater detail in Chapters 5 and 24, AP and dynamic hyperinflation vary with those changes that influence the expiratory time constant (resistance and compliance) or the time available for deflation (minute ventilation and expiratory time fraction) (Fig. 9-12). Thus, although classically a problem of patients with severe airflow obstruction, AP can arise in patients with any lung mechanics profile—even ARDS—where tidal gas trapping, primarily in dependent zones, is a product of compressive airway closure, increased airway edema, and high minute ventilation (Fig. 9-12). Obese patients tend to trap gas during tidal deflation when recumbent but less so when upright. To reduce AP, it is helpful to reduce minute ventilation requirement, improve expiratory flow resistance, and lengthen the percentage of the ventilatory cycle spent in expiration. (When induction and maintenance of AP is the intent, as during inverse ratio ventilation or APRV, just the opposite strategy is followed. See Chapter 7.) Despite many physiological similarities, PEEP and AP are not interchangeable with respect to pressure uniformity. The distribution of AP is often quite heterogeneous, even within the same patient. Many units occluded at end-expiration, for example, are located in dependent regions. Moreover, distention of individual lung units is a direct function of their own compliance.

**FIGURE 9-12.** Mechanisms and implications of auto-PEEP (AP). AP can be generated in normal lung units because of increased ventilation (upper right), one-way or ball valving (as by a secretion plug, lower right), or a lengthy expiratory time constant with collapsible airways and expiratory flow limitation (center). Gas trapping with AP can also result from airway compression by heavy lungs or obesity (upper left) or from high resistance in airways that are not compressible (lower left). Thus, the same AP value may or may not be associated with
hyperinflation, depending on the mechanism for time constant (resistance × compliance) prolongation.

Unsuspected, this auto-PEEP effect can seriously reduce true cardiac filling pressures and confound interpretation of pulmonary artery and wedge pressures, raising them by an amount similar to the pressure transmitted to the pleural space (see Chapters 2 and 5). Because AP must be reversed before inspiratory airflow can begin or the ventilator can be triggered, the ventilatory workload also rises in spontaneously breathing patients. The detection, consequences, and management of AP are discussed in greater detail in Chapters 2, 5, and 25.

**PEEP on Auto-PEEP**

Although PEEP is the sum of applied PEEP and AP, adding PEEP to existing AP may not raise total PEEP proportionately when expiration is flow limited during tidal breathing (Fig. 9-13 and Chapter 5). Substituting PEEP for AP may help even the distribution of ventilation, improve triggering sensitivity, reduce the work of spontaneous breathing, or increase the tidal volume when pressure support or pressure control is used.

**FIGURE 9-13. The effect of PEEP on AP in a patient with expiratory flow limitation during tidal breathing.** AP represents a positive end-expiratory alveolar pressure (P_{alv}) that must be overcome by inspiratory effort (reflected by esophageal pressure, P_{es}) before the ventilator can be triggered or spontaneous breathing can begin. PEEP similar to the original AP added downstream from the site of flow limitation does not slow expiratory airflow significantly. As AP is counterbalanced, the inspiratory work of breathing declines. PEEP, positive end-expiratory airway pressure. (Modified from Smith TC, Marini JJ. Impact of PEEP on lung mechanics and work of breathing in severe airflow obstruction: the effect of PEEP on auto-PEEP. J Appl Physiol. 1988;65[4]:1488-1499, with permission.)

**SUGGESTED READINGS**


• Key Points

1. Continuing need for ventilator assistance may arise from oxygen desaturation of hemoglobin during spontaneous breathing, cardiovascular instability during machine withdrawal, psychological dependence, or most commonly, imbalance between ventilatory capability and demand.

2. The minute ventilation requirement is a key determinant of the power needed to sustain breathing. Three primary factors determine the minute ventilation requirement: the CO\(_2\) production, the efficiency of ventilation, and the central drive to breathe.

3. Ventilatory power is the product of minute ventilation and the mechanical work of breathing per liter of ventilation. For any specific tidal volume and flow rate, the primary determinants of the inspiratory work per liter of ventilation are the resistance and elastance of the respiratory system and auto-positive end-expiratory pressure, a reflection of dynamic hyperinflation.

4. Ventilatory capability is determined by the central drive to breathe and the bulk, strength, and endurance of the ventilatory muscles, which deteriorate during sustained inactivity. Conversely, the induction of fatigue by excessive effort may impair muscular performance for at least 12 to 24 hours afterward. Sleep is essential for optimal neuromuscular performance and for preparing the patient for independent breathing.

5. Prediction of success or failure of a weaning trial involves the assessment of oxygen exchange efficiency, cardiovascular status, and muscular endurance. Although individual measures of strength, gas exchange, or workload aid in this assessment, “integrative” weaning indices observed during a brief trial of unaided breathing (e.g., rapid shallow breathing index, interpreted in conjunction with minute ventilation and chest compliance) as well as integrative tests of ventilatory reserve (breathing pattern variability, cough-induced inspiratory capacity) are perhaps the most physiologically sound indicators. Expiratory performance is especially important to evaluate when there is a high secretion load requiring expectoration.

6. Persistent failure to discontinue ventilation despite adequate respiratory parameters should prompt consideration of cardiac ischemia, congestive heart failure, psychological dependence or delirium, gas exchange deterioration, lingering effects of sedation, or other nonrespiratory explanation for the failure. A commonly overlooked culprit is net fluid balance that is markedly positive.

7. After the patient has been optimally prepared, the withdrawal sequence involves estimation of the likelihood of success, a trial of spontaneous ventilation, gradual withdrawal of ventilatory assistance (when indicated), a brief period of observation with minimal pressure support, extubation, and close follow-up after ventilator discontinuance and extubation.

8. Patients experiencing protracted difficulty during removal of ventilatory support should receive adequate ventilator assistance at night to permit sleep. The patient must never be forced to work beyond his or her ability to comfortably sustain it.

9. Reintubation occasionally is necessary in the first few days after extubation. These delayed weaning failures usually arise because of an inability to swallow normally (resulting in oropharyngeal aspiration), glottic swelling, inability to clear thick airway secretions, or congestive heart failure. Appropriate precautions taken during this period may avert failure. Noninvasive ventilation and high-flow nasal
oxygen may provide a useful bridge across this difficult transition.

10. Tracheostomy tube extraction should be considered when the patient no longer requires frequent airway suctioning, high inspired fractions of O\textsubscript{2}, or periodic (nocturnal) connection to the ventilator. Conversion to noninvasive ventilation and/or assisted coughing is possible for many patients previously assigned to permanent tracheostomy.

PHYSIOLOGIC DETERMINANTS OF VENTILATOR DEPENDENCE

Stages of Ventilator-Supported Breathing

Once the underlying reason for initiating ventilator support has been successfully addressed, many patients tolerate abrupt termination of mechanical assistance without needing to gradually adjust to spontaneous breathing. However, evaluating readiness is always a clinical judgment, and in that minority of patients for whom withdrawing machine support proves difficult, a strategy for transferring the respiratory workload to the patient must be developed (Table 10-1). Weaning is the graded removal of ventilator support from patients who cannot tolerate immediate conversion to fully spontaneous breathing. Some argue convincingly that the only thing that really needs to be done is to check readiness for spontaneous breathing. Nonetheless, the weaning process often takes place in several stages: independence from positive pressure ventilation, weaning from positive end-expiratory pressure (PEEP), extraction of the endotracheal (ET) or tracheostomy tube, and discontinuation of supplemental oxygen.

A continuing need for breathing assistance may arise from O\textsubscript{2} desaturation of hemoglobin during unaided breathing, cardiovascular instability during machine withdrawal, psychological dependence, or imbalance between ventilatory capability and demand. Normal diurnal rhythms and homeostatic controls are frequently inoperative or impaired. Often, several of these causes operate simultaneously.

<table>
<thead>
<tr>
<th>Table 10-1. Who Benefits from Gradual Withdrawal of Machine Support?</th>
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</table>
| - If workload is disproportionate to capability  
  - Muscle reconditioning  
  - Reintegration of ventilatory coordination (?)  
- If sudden transitions are physiologically or psychologically stressful  
  - “Panic” cycles in airflow obstruction  
  - Congestive heart failure  
    - Autotransfusion  
    - ↑O\textsubscript{2} consumption  
    - Diastolic dysfunction  
  - Coronary ischemia  
  - Arterial hypoxemia |

Psychological Factors

Prolonged mechanical ventilation is a harrowing experience that may elicit anxiety, depression, or psychosis. Delirium, manifested by inattentiveness, paranoid behavior, and disorientation, occurs very commonly in sleep-
deprived and elderly patients receiving medications that interfere with normal mental functioning (e.g., corticosteroids, benzodiazepines). A careful evaluation of mental status often is fruitful, because cooperation and avoidance of panic reactions during the weaning attempt may depend on control of the delirium. Ensuring sleep, reorienting discussion, and appropriate use of psychotropic agents (e.g., haloperidol, quetiapine, dexmedetomidine) can speed up the process (see Chapter 17).

**Arterial Hypoxemia**

Mechanical ventilation can improve arterial oxygenation by providing large tidal breaths that oppose atelectasis, sealing the airway to allow delivery of high inspired concentrations of oxygen and PEEP, reducing or offsetting the effects of pulmonary edema, improving the output requirements and loading conditions of a compromised heart, and improving the balance between tissue oxygen delivery and demand. Under a high breathing workload, the respiratory muscles consume a great deal of oxygen. Vigorous expiratory activity reduces end-expiratory lung volume. Stressful breathing may also increase the oxygen demand of other organs by causing agitation or discharge of catecholamines. When cardiac output is compromised, this increased oxygen demand may force greater O$_2$ extraction. The admixture of the desaturated mixed venous blood that results may then contribute to hypoxemia. Moreover, increased metabolic demands may cause myocardial decompensation, ischemia, or diastolic dysfunction.

Mechanical ventilation mitigates these problems by relieving much of the ventilatory workload.

**Cardiovascular Instability**

Resuming a high ventilatory workload often presents a cardiovascular challenge in the setting of ischemic disease, heart failure, or reduced cardiac reserve. Inappropriately low cardiac output can contribute directly to hypoxemia and weakness of the ventilatory pump. Cardiovascular instability overtly limits the pace of ventilator withdrawal

when chest pain, diastolic dysfunction, or arrhythmias develop during the reloading of the respiratory pump. Hypoxemia, abruptly altered cardiac loading conditions, and stress-related release of catecholamines frequently provoke rhythm disturbances in the transition to spontaneous breathing. Resuming spontaneous breathing simultaneously increases both preload and afterload of the left heart, as well as increases anxiety and the respiratory burden. The need for O$_2$ delivery can impressively increase at a time when the heart is least able to provide it and may trigger coronary ischemia. It is prudent to optimally prepare patients predisposed to coronary ischemia before attempting the stresses of independent breathing.

Oxygen administration, establishing electrolyte and pH balance, antiarrhythmic therapy, afterload reduction, anti-ischemic measures, diuresis, and more gradual conversion to fully spontaneous breathing may be instrumental to the success of machine withdrawal. For patients with coexisting airflow obstruction, assuming a high ventilatory workload associates with a fall (rather than a rise) in mean intrapleural pressure. As forceful inspiratory efforts lower intrathoracic pressure, central vascular congestion and left ventricular afterload increase (Fig. 10-1). In such circumstances, it is essential to reduce total ventilatory demands by measures that improve lung mechanics and reduce minute ventilation. The use of continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV) may be strikingly effective. Pharmacotherapy to improve cardiac performance and/or relieve ischemia before weaning is often helpful.
FIGURE 10-1. Influence of spontaneous breathing on left ventricular filling pressure in patients with airflow obstruction. After an abrupt transition to spontaneous breathing, the increased effort results in marked decline of pleural pressure. Transmural wedge pressure increases as mean intrapleural pressure falls (A). For patients with left ventricular failure, the increased afterload and oxygen consumption may dramatically elevate transmural wedge pressure, producing pulmonary congestion.

Imbalance of Ventilatory Capability and Demand
To sustain spontaneous ventilation, both ventilatory drive and endurance must be adequate. Impaired ventilatory drive often contributes to CO₂ retention or hypoxemia, especially when excessive sedation or chronic hypercapnia is present. The most common reason for ventilator dependence, however, is the inability to maintain appropriate ventilation without intolerable dyspnea. Ventilatory workload is determined by the product of minute ventilation requirement \( \dot{V} \) and the energy expended per liter of gas flow.

Ventilatory Demand: Minute Ventilation Requirement
Reducing the minute ventilation requirement is an important goal because \( \dot{V} \) bears a direct relationship to the work of breathing. Three primary factors determine the \( \dot{V} \) requirement: the
CO₂ production, the efficiency of ventilation, and the sensitivity of the central drive mechanism (Table 10-2).

CO₂ Production

Fever, shivering, pain, agitation, increased work of breathing, sepsis, and overfeeding are common causes of increased CO₂ production in the intensive care unit (ICU). In the weaning phase, cautious anxiolysis and pain relief can dramatically reduce the ventilatory requirement. Carbon dioxide production is also influenced by underlying nutritional status, as well as by the number and composition of the calories administered. The semistarvation that often precedes critical illness suppresses CO₂ production. Despite the importance of adequate nutrition, patients should not be overfed. Excess calories may be converted to fat, generating CO₂ as a metabolic by-product unlinked to energy production. Carbohydrate evolves more CO₂ per calorie than fat or protein. However, even though large calorie loads can contribute to ventilatory failure, the importance of calorie composition to ventilator dependence remains to be shown convincingly. Overfeeding also may lead to abdominal distention and discomfort that may adversely impact a patient poised at the boundary of ventilatory failure.

<table>
<thead>
<tr>
<th>CO₂ Production</th>
<th>↑ V₉/V₉</th>
<th>↑ Drive</th>
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<tbody>
<tr>
<td>Fever</td>
<td>Lung disease</td>
<td>Neurogenic</td>
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<tr>
<td>Shivering</td>
<td>Hypovolemia</td>
<td>Psychogenic</td>
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<tr>
<td>Pain/agitation</td>
<td>Vascular occlusion</td>
<td>Metabolic acidosis</td>
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<td>Trauma/burns</td>
<td>External apparatus</td>
<td>Hypoxemia</td>
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<tr>
<td>Sepsis</td>
<td>Excessive PEEP</td>
<td>Reflex stimuli</td>
</tr>
<tr>
<td>Overfeeding</td>
<td>Excessive [V with dot above]ₑ target for small (“baby”) lung</td>
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Table 10-2. Factors Affecting Ventilatory Demand

Ventilatory Efficiency

Alveolar ventilation (Vₐ), the component of ventilation that eliminates CO₂, is the total minute ventilation adjusted for the fraction of wasted ventilation. Breathing efficiency can be characterized by the following expression:

$$V_a = \dot{V}_E \left(1 - \frac{V_D}{V_T}\right)$$

where V₀/V₉ is the physiologic dead space fraction (see Chapter 5). Virtually, all of the diverse processes that damage the lung or airways of the critically ill patient increase the wasted fraction of ventilation. Certain reversible factors unrelated to underlying lung pathology also can prove to be important. For example, thromboembolic or vasculitic pulmonary arterial occlusion, excessive PEEP, and hypovolemia may reduce perfusion to the ventilated lung, expanding the alveolar dead space. Small tidal volumes are characterized by a high anatomic dead space percentage. Adding “apparatus dead space,” disposable heat and moisture exchangers and other devices or tubing interposed between the ET tube and the “Y” of the ventilator circuit may contribute marginally to ventilatory inefficiency.

Central Drive
Although it is unusual for a patient to remain persistently ventilator dependent solely because of a lack of breathing effort, inappropriately depressed or enhanced drive to breathe may limit weaning progress. As a rule, elderly and debilitated patients are the most susceptible to drive suppression. Suppressed ventilatory drive may be explained by neurologic impairment, hypothyroidism, lingering sedation (commonly the predominant cause), sleep deprivation, poor nutrition, and metabolic alkalosis (primary or compensatory). Starvation impairs hypoxic and, to a lesser extent, hypercapnic sensitivity. Interestingly, drive is restored rapidly within a few days of reinitiating adequate feeding, perhaps in advance of improved muscle function. The drive to breathe is generally higher in the waking state. When infused benzodiazepines are given continuously for days to weeks, sufficient drug and drug metabolites may store in the brain and fat tissues to suppress consciousness and/or drive for long periods after they are discontinued (occasionally as long as 7 to 10 days). Such unintended effects argue forcefully for intermittent, “only as needed” sedation and the practice of once daily interruption of continuous sedation to assess the need for and rate of their ongoing use. Pharmacologic stimulants to wakefulness (e.g., modafinil) are occasionally helpful, but drugs to selectively improve drive to breathe are not currently available.

Enhanced central drive arising from neurogenic, psychogenic, reflex, or metabolic stimuli augments ventilatory demand and workload. In asthma and acute pulmonary edema, drive-stimulating reflexes arising from the lung or chest wall downregulate after correction of the underlying disorders. Hypoxemia, hypotension, developing sepsis, and acidosis also accentuate ventilatory demands. Correction of metabolic acidosis is one of the most important ways to reduce central drive. It is also important not to force PaCO\textsubscript{2} much below the patient's usual resting value, as the ensuing bicarbonate diuresis redefines the $\dot{V}$ needed to maintain cerebral pH homeostasis. In fact, keeping PaCO\textsubscript{2} somewhat higher than the chronic value for that patient may help minimize the $\dot{V}$ requirement.

Pain relief is mandatory, and opiates are all that many (if not most) patients require. Anxiety and disorientation influence ventilatory demand and often can be addressed successfully by counseling, co-opting the patient into the weaning plan, and cautious use of anxiolytics or major tranquilizers. Haloperidol (Haldol) is a good first option but often proves inadequate. Quetiapine (Seroquel), risperidone, olanzapine (Zyprexa), and occasionally Depakote may work for delirious or combative patients when more usual approaches fail. The ECG must be monitored, however, to avert the possibility of dangerous QT prolongation and arrhythmia induction. Dexmedetomidine (Precedex) is an infused sedative that does not markedly suppress consciousness or drive to breathe. Given the difficulty of removing the dissociative sedatives (e.g., lorazepam, midazolam) without precipitating delirium, such properties often prove useful in weaning applications. Boosting the inspired O\textsubscript{2} fraction is often an effective way to reduce drive and helps interrupt a panic reaction accompanied by worsening hypoxemia.

**Ventilatory Demand: Work Per Liter of Ventilation**

**Intrinsic Factors**

Ventilatory power is the product of $\dot{V}$ and mechanical work of breathing per liter of ventilation. The quotient of this mechanical workload and neuromuscular efficiency defines how much energy must be expended in breathing. Once tidal volume and inspiratory time are set, the frictional and elastic properties of the respiratory system determine the pressure generated per breath, as well as the external work output per liter of ventilation. The average inspiratory pressure developed by the unaided respiratory system per breath can be approximated by a simple formula:
where $R$ and $C_{RS}$ are the inspiratory resistance and compliance of the respiratory system, $V_T$ is tidal volume, and $t_i$ is the time required for inspiration (see Chapter 5 and Fig. 10-2). Therefore, for the same level of $[V \text{ with dot above}]_E$, more external work must be done if $C_{RS}$ falls or if $V_T$, auto-PEEP, mean inspiratory flow ($V_T / t_i$), or $R$ increase. Bronchospasm, retained secretions, and mucosal edema are the primary reversible factors that increase $R$. Retained secretions greatly amplify the inspiratory workload in patients with already narrowed airways. Lung edema and infiltration, high lung volumes, pleural effusions, abdominal distention, and supine posture may reduce $C_{RS}$. Air trapping and auto-PEEP are highly dynamic phenomena influenced powerfully by minute ventilation and the ease with which gas empties from the lungs (see Chapter 25). Auto-PEEP varies with changes in the breathing impedance (e.g., bronchospasm, secretion retention, minute ventilation, body position, alteration of inspiratory time fraction, and expiratory muscle activity).

These are not the only factors that determine the energy needed by the respiratory muscles, however. For the same tidal volume, the respiratory muscles consume more oxygen (become less effective) when they begin inspiratory contraction from a mechanically disadvantageous high lung volume or when the pattern of muscle contraction is poorly coordinated. For example, supine patients with diaphragmatic weakness may allow the abdominal contents to be drawn upward with each inspiratory effort, so that much of the tension developed by the inspiratory muscles of the chest cage fails to translate into the negative pleural pressure that draws air into the lungs.
Extrinsic Factors

The external properties of the ventilator circuit also can play an important role in determining the ventilatory workload. ET tube resistance exceeds the normal resistance of the upper airway. Frictional pressure losses increase rapidly when high flows are driven through small-caliber tubes. Kinks and (less commonly) airway secretions may encroach on an otherwise adequate lumen. In some instances, it may be wise to attempt extubation, exchange an orotracheal tube for a larger one (e.g., via a tube changer; see Chapter 6), or replace a nasotracheal tube with an orotracheal one. Tracheostomy is worth considering to reduce resistance and to facilitate extraction of airway secretions in particularly difficult patients. In theory, all pressure support ventilation (PSV) and CPAP should be minimized or withdrawn before extubation to test the marginal patient's ventilatory reserve (the “T-piece trial,” see following). Even in marginal candidates, however, extubation from modest pressure support and CPAP often succeeds, especially when the patient bites the tube or experiences extreme discomfort or a narrow bore tube hinders airflow.

Tracheostomy offers larger tube diameter, shorter axial length, lower resistance, and improved secretion clearance. The resistance of other circuit components (e.g., HME) varies widely but infrequently adds significantly to the ventilatory burden. Although the expiratory valves of older machines frequently presented problems, they are rarely limiting when using modern equipment.

Ventilatory Capability

The ability to sustain the effort of breathing is determined by respiratory drive, muscle strength, and endurance.

Central Drive

Although it is unusual for a patient to remain persistently ventilator dependent solely because of a lack of breathing effort, multiple interacting and potentially correctable factors suppress the output of the ventilatory drive center, as discussed earlier. Drive stimulants used in decades past, such as doxapram or progesterone, are seldom helpful or used.

Muscular Performance

STRENGTH

With normal ventilatory drive, carbon dioxide retention is uncommon if the patient can generate more than 25% of the predicted maximum inspiratory pressure against an occluded airway. The strength of the respiratory muscles is determined by muscle bulk, the intrinsic properties and loading conditions of their contractile fibers, and the chemical environment in which the muscle contracts. Poor nutrition causes muscle wasting and thereby limits maximal respiratory pressures. As overall body weight diminishes, the mass and strength of the diaphragm decrease proportionately. Paralysis that is sustained for more than 24 to 48 hours can initiate the process of diaphragm atrophy. Glucocorticoids accelerate the rate of protein catabolism. Concentrations of calcium, magnesium, potassium, phosphate, hydrogen ion, chloride, and carbon dioxide influence muscle performance. Hypoxemia tends to impair endurance more than muscle strength.

Certain commonly used drugs—particularly aminoglycosides and antiarrhythmics (e.g., calcium channel blockers)—contribute to weakness in the setting of myasthenia gravis or other underlying neuromuscular impairment (see Chapter 17). Conversely, aminophylline and β-sympathomimetic drugs may modestly improve contractility and endurance. Intriguing experimental data suggest that the resting potential of the skeletal muscle membrane may remain abnormal for days after sepsis control and perhaps after the crisis periods of other critical illnesses as well. Moreover, a “critical illness neuropathy” may help explain the prolonged and impressive muscle
weakness observed in many of these patients long after the acute phase has passed. The extended suppression of neuromuscular excitation by paralytic agents may result in very profound weakness for lengthy periods after they are discontinued, especially when corticosteroids have been used concomitantly, as in status asthma (see Chapter 17).

**CONTRACTILE FIBER PROPERTIES**

The contractile force developed by a stimulated muscle fiber relates directly to its resting length at the onset of contraction and inversely to its speed of contraction. Force output is, therefore, compromised when a patient inhales rapidly from high lung volume, as so often occurs in breathless, hyperinflated patients with chronic obstructive pulmonary disease (COPD) or asthma (see Chapter 25).

**ENDURANCE**

Endurance, the ability of a muscle to sustain effort, is determined by the balance between the supply and demand of muscular energy. Hypoxemia, profound anemia, and ischemia are especially important to correct, because working muscles require an adequate flow of well-oxygenated blood for optimal performance. Although the respiratory muscles normally can access a large recruitable reserve, even this luxuriant supply may be insufficient under conditions of high stress and a failing cardiac pump. Studies of patients with acute ventilatory failure indicate that spontaneous breathing routinely consumes approximately 25% of the oxygen used by the entire body and even more during flagrant respiratory distress. (The normal percentage at rest is 1% to 2%.)

Over the years, many attempts have been made to gauge endurance by comparing spontaneous breathing cycles with maximal voluntary efforts. For example, the ability to voluntarily double $V'\theta$ or tidal volume has been considered a positive predictive sign.

Unfortunately, such voluntary indices require patient cooperation. However, the respiratory pattern gives important clues to ventilatory compensation. The respiratory frequency is the most sensitive but least specific indicator of developing problems. Early in the course of respiratory muscle fatigue, respiratory frequency increases. At the threshold of total exhaustion, frequency may diminish—a harbinger of approaching apnea. The breathing pattern shows variation of tidal volume and I:E ratio when the patient who receives modest support has ample respiratory reserve. In responding to an increased ventilatory workload (e.g., increasing exercise), a well-compensated subject will regularize the breathing pattern and increase both frequency and tidal volume together. Although tidal volume may reach a plateau value while frequency is still rising, tidal volume does not fall during compensated exercise and the ratio of frequency to tidal volume rarely exceeds 50 breaths/min/L in the healthy individual, even during vigorous exertion. It has been suggested that a ratio of frequency to tidal volume that exceeds approximately 100 breaths/min/L indicates an unsustainable workload, as the patient fails to generate sufficient pressure to achieve a tidal volume appropriate to the minute ventilation required. The result is inefficient gas exchange and, ultimately, failure to wean from ventilatory support. (There are many exceptions, however, as most patients with restrictive disease naturally start from a higher resting baseline.)

Other components of the respiratory pattern, although harder to quantify, provide equally valuable diagnostic clues. At moderate levels of exertion, pressure in the abdomen rises as the diaphragm contracts, displacing the abdominal contents downward and outward; expiration, which occurs passively at low levels of exertion, often becomes active. Vigorous activity recruits the thoracic musculature, elongating the chest and expanding the rib cage. If diaphragmatic contraction is not proportionately forceful, the abdomen may appear to retract inward during inspiration. When observed in the supine position, this phenomenon, known as paradoxical abdominal motion, indicates a high level of exertion relative to the capability of the diaphragm. Paradoxical abdominal motion may be observed routinely in well-compensated patients with severe airflow obstruction. Some clinicians view the development of this finding as an indicator of established muscle fatigue, but more likely, it should be
interpreted as a sign of high workload that may or may not be tolerable. Much less commonly, the ribcage and abdomen alternate primary responsibility for driving inspiration, a pattern known as respiratory alternans. Overt respiratory alternans is much less commonly observed than paradoxical abdominal motion and, when present, often has a neuropathologic origin.

**IMPORTANCE OF MUSCLE REST**

To reverse fatigue, the most effective intervention is to rest the muscles. Total rest is not required but a substantial fraction of the imposed workload must be relieved. Assisted mechanical ventilation, optimally adjusted to meet patient demands and avoid asynchrony, usually allows the patient to rest sufficiently. As a rule, the support level can be assumed adequate if the alert patient is made comfortable. How long a skeletal muscle must be rested before it fully recovers from fatigue is not known with certainty. However, physiologic evidence of subnormal performance can be detected in the laboratory setting for at least 12 to 24 hours after brief exposure to a fatiguing load. Therefore, a rest period of at least 12 to 24 hours seems appropriate after an episode of acute decompensation. Because recovery may be prolonged, labored breathing risks fatigue and must be avoided.

**PREDICTING INDEPENDENCE FROM VENTILATORY SUPPORT**

Many predictive indices based on ventilatory performance have been suggested to accurately forecast the outcome of the weaning trial (Table 10-3). However, if the patient is ventilator dependent for reasons unrelated to muscle strength (e.g., hypoxemia, cardiac ischemia, or psychological factors), such indices are of questionable value. Their predictive performance is equally limited after a long period of ventilatory support and for certain patients with permanent neuromuscular deficits. Even when impaired ventilatory power and endurance are responsible, no single index has been universally successful, perhaps because multiple factors cause the patient to remain ventilator dependent. Widely used panels of indicators tests are $[\dot{V}_{E}]$, muscle strength, muscle reserve, and respiratory mechanics. Patients who are successfully weaned from mechanical support generally have a $[\dot{V}_{E}]$ lower than 10 L/min, a maximally negative inspiratory pressure exceeding -20 cm H$_2$O, a vital capacity (VC) more than twice the spontaneous tidal volume, and an ability to double the baseline $[\dot{V}_{E}]$ on command. In practice, the problem with using such a panel of criteria is twofold: only selected components can be measured in uncooperative patients, and there is uncertainty when only one or two indices lie within the acceptable range. Thus, although these time-honored criteria are reliably predictive when all are satisfied or violated, they are of questionable assistance in difficult cases. Although favorable weaning parameters may support a decision to undertake a weaning attempt, discouraging values should not preclude a carefully observed trial of spontaneous breathing or an attempt to wean if clinical judgment otherwise suggests a favorable outcome (Table 10-4).

<table>
<thead>
<tr>
<th>Table 10-3. Predictors of Weanability (Minimum Requirements)$^a$</th>
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<tr>
<td>Ventilation</td>
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<td></td>
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<tr>
<td>$[\dot{V}_{E}]$</td>
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<td>10-15 L/min$^b$</td>
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<td>[V with dot above]$^E$ ≤ 175 mL/kg/min</td>
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<td>aFor abbreviations, see text.</td>
</tr>
</tbody>
</table>

### Table 10-4. Evaluation for Weaning

**Awake, Oxygenated, Stabilized?**

- **Power requirement**
  - Minute ventilation
  - Work per liter (mean airway pressure)
- **Power reserve**
  - Cough inspiratory capacity (catheter or saline stimulation)
  - Prior variability of minute ventilation (over 6-8 h)
    - Compare sleep vs. awake $V_E$
- **Spontaneous breathing trial**
  - Variation of tidal volume, $V_E$, I:E ratio
  - Assess $f/V_T$ ratio in relation to:
    - Respiratory compliance, chronic neuromuscular background
    - *Directional* change in minute ventilation

### Noninterventional Measures

**Arterial Blood Gases and Pulse Oximetry**

Although not reliable predictive indices per se, arterial blood gases and pulse oximetry are invaluable aids in gauging the progress of a weaning trial, especially when trends are followed. Observations of breathing pattern and muscle activity (see below) as well as expiratory capnometry are also valuable.

**Minute Ventilation**

Ventilatory requirement and patient capability can be assessed crudely by $V_E$ and the maximal inspiratory
pressure ($P_{\text{max}}$ or MIP) generated against an occluded airway. Although $V_E$ is easy to measure, it should be interpreted with regard for body habitus, metabolic rate, and pH. For example, a 50-kg patient with respiratory acidosis at the time of $V_E$ measurement may have a minute ventilation of only 10 L/min and yet be unable to resume spontaneous unaided breathing. Conversely, a patient weighing 100 kg with respiratory alkalosis may wean easily at the same level. As valuable as $V_E$ may be, it only partially characterizes ventilatory demand; work per liter of ventilation is equally important in this assessment, as already discussed. Just as importantly, demand always must be related to capability. Low minute ventilation during sleep (as opposed to waking) is a good sign that underlying physiologic demands for ventilation are modest.

**Spontaneous Breathing Pattern**

Well-compensated patients breathing with pressure support demonstrate considerable variability in tidal volume and $I:E$ ratio. Patients who are well adjusted to the ventilatory workload also choose tidal volumes greater than 4 to 5 mL/kg of lean body weight and breathing frequencies lower than 30/min. Although each breath taken with a shallow tidal volume is less energy costly than a deeper breath, the total energy expenditure necessary to maintain a given $\text{PaCO}_2$ may be similar or even greater, inasmuch as anatomic dead space occupies a larger percentage of each breath during shallow breathing. Therefore, patients with relatively normal chest mechanics who must breathe at frequencies greater than 35/min usually do so because they are too weak or fatigued to inspire to an appropriate depth. Some patients with neurologic disease or severe chronic restrictive disease (e.g., massive obesity, kyphoscoliosis, interstitial fibrosis) assume rapid shallow patterns because of disordered ventilatory control or reflex stimulation and may wean successfully at frequencies exceeding 40/min. The breathing pattern assumed during a brief (5-minute) trial of spontaneous breathing under direct observation as well as its progression over that interval has proved to be an excellent integrative test of endurance (Fig. 10-3).

It is important to understand that for many patients, a high and steady $f/V_T$ ratio (often referred to as the rapid shallow breathing index [RSBI]) may simply reflect the natural “exercise” response to the increased workload of spontaneous breathing or anxiety. A rising $f/V_T$ in conjunction with an elevating minute ventilation means something quite different from the same high but rising $f/V_T$ and a declining minute ventilation—compensated exercise response versus evolving ventilatory failure. As always, the appearance of the patient provides essential corroborating information.
FIGURE 10-3. Rapid shallow breathing and the ratio of frequency to tidal volume ($f/V_T$) in a patient with airflow obstruction. Upon ventilator disconnection, a poorly compensated patient with airflow obstruction tends to increase the work of breathing, develop gas trapping (auto-PEEP), and responds by decreasing tidal volume and increasing respiratory frequency. Although many exceptions exist, a patient recovering from acute illness with an $f/V_T$ ratio exceeding 100 breaths/min/L during spontaneous breathing is less likely to be weaned successfully from ventilatory support.

**Voluntary Measures**

**Maximal Inspiratory Pressure**
Maximal inspiratory pressure must be measured carefully to be of value. Although highly negative numbers encourage a weaning attempt, low values may reflect inadequate measurement technique rather than true patient weakness. For poorly cooperative patients, airway occlusion must start from a low lung volume and continue for at least 8 to 10 efforts before the value is recorded. (A one-way valve that selectively prevents inspiration while allowing unimpeded expiration may be helpful to elicit maximal response.) The MIP, a good measure of isometric muscle strength, by itself does not yield reliable information regarding endurance. This is better gauged by integrative indices of workload and response (see below).

**Vital Capacity and Inspiratory Capacity**
Considerably less muscular effort is required to achieve the VC or its inspiratory component (IC) than to achieve a valid MIP. Although a one-way valving system can be used effectively to estimate the VC by tidal “breath stacking” without patient cooperation, this involuntary approximation reflects respiratory system mechanics more closely than it does muscle strength and is seldom used in the clinical setting. If a cooperative patient achieves a (single effort) vital or inspiratory capacity twofold greater than the tidal volume, the chances are good that ventilatory reserves are sufficient to allow successful resumption of spontaneous breathing. A near inspiratory capacity effort can often be elicited during a vigorous cough provoked by an airway suction catheter or saline instillation. Because modern ventilators have “closed” suction capability and continuously display volumes associated with tidal efforts, a good indication of the patient's IC and VC can be easily assessed.
Cough, Expiratory Pressure, and Maximal Expiratory Flow

Measures aimed at assessing the forcefulness of expiration may be important in gauging the ability to cough and clear secretions and, therefore, the need for continued intubation but have a more limited place in assessing the likelihood of successful weaning from the ventilator (see below).

Other Useful Measures

Nonrespiratory factors (e.g., coronary ischemia) often predominate in the most difficult weaning cases. Observations apart from standard indices of lung mechanics correlate well with an adverse weaning outcome. Very low or high pulse rates, respiratory rates greater than 30/min, forceful abdominal contractions, accessory muscle activity, chaotic breathing patterns, and coma are all negative prognostic factors. When uncertainty exists regarding upper airway patency, the ability of gas to flow around the ET tube after cuff deflation is reassuring (but not definitive) evidence that vocal cord dysfunction or critical structural narrowing are not present. The oral, retropharyngeal, and supraglottic areas must be suctioned free of secretions prior to conducting the cuff deflation test. A PEEP setting that exceeds 15 cm H$_2$O helps assure that failure of air leakage around the deflated cuff is not due to a mucus seal. Because the tube splints the glottis open, passing these tests, although comforting to the clinician, does not ensure that variable (functional) upper airway obstruction will not occur in the postextubation period.

Table 10-5. Clues for Predicting “Weanability”

- Correlate rapid shallow breathing index (RSBI) with $[V_{dot above}]_E$
  - If $[V_{dot above}]_E$ and RSBI both increase → exercise response
  - If $[V_{dot above}]_E$ does not rise, increasing RSBI suggests problems
- Observe variation of breathing patterns
  - $[V_{dot above}]_E$ before trial
  - Pattern of breathing on low level of PSV
- Observe “cough inspiratory capacity”
  - If >2 × $V_T$ → good power reserve

Integrative Weaning Indices

Several clues to the readiness of the patient for ventilator discontinuation are available in the hours preceding the spontaneous breathing trial (Table 10-5). Among the most valuable of these are a minute ventilation that falls during sleep independently of sedation, a nontachycardic sinus rhythm, and a variable breathing pattern characterized by near normal minute ventilation and a wandering $I:E$ ratio. A cough-induced IC that is two to three times the tidal volume is also encouraging. It should be kept in mind that the minute ventilation should be referenced to body size. Any single prognostic indicator is unlikely to prove successful unless it closely reflects the balance of ventilatory capability and demand. Analysis of the ventilating pattern during a trial of spontaneous breathing is attractive, in that it allows the brain to integrate the information necessary to relate the workload to work capacity. Among the available options (Table 10-6), the frequency-to-tidal volume ratio ($f/V_T$) is perhaps the most useful and readily calculated. A value exceeding 100 breaths/min/L during the first minute of spontaneous breathing indicates extraordinarily rapid (reflected by $f$) and shallow (reflected by $1/V_T$) breathing. Clearly, patients with restrictive disorders
of the lungs or chest wall should logically adopt a relatively rapid shallow pattern to minimize energy expenditure.

Justified concern has been raised over the accuracy of this index for patients with underlying severe airflow obstruction, neuromuscular disorders, or chest wall deformity. It is unclear whether any such index based on respiratory mechanics can reliably reflect cardiac dysfunction or hypoxemia occurring as a consequence of spontaneous breathing effort. However, more complex indexes do not seem to offer major advantages over the \( \frac{f}{V_T} \) ratio. An \( \frac{f}{V_T} \) that rises steadily during the breathing trial is a negative prognostic sign.

### Table 10-6. Integrative Weaning Indices

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \frac{P_{max}}{\Delta P_{10}} &lt; 0.4 ) (sustainable) tidal breath pressure</td>
<td></td>
</tr>
<tr>
<td>( \frac{P_{max}}{\Delta P_{10}} \times \frac{t_i}{t_{tot}} &lt; 0.15 ) (sustainable pressure-time product)</td>
<td></td>
</tr>
<tr>
<td>( P_{0.1} &lt; 4 \text{ cm H}_2\text{O} )</td>
<td></td>
</tr>
<tr>
<td>( \text{CO}<em>2)-stimulated increase of ( P</em>{0.1} &gt; 4 \text{ cm H}_2\text{O} )</td>
<td></td>
</tr>
<tr>
<td>( \frac{f}{V_T} &lt; 100 )</td>
<td></td>
</tr>
<tr>
<td>( V_T/VC &lt; 0.5 )</td>
<td></td>
</tr>
<tr>
<td>( \frac{[V \text{ with dot above}]}{MVV} &lt; 0.5 )</td>
<td></td>
</tr>
</tbody>
</table>

\( MVV \), maximum voluntary ventilation.

### WEANING TRIAL

#### Preparations for Withdrawing Ventilatory Support

Most patients are easily liberated from mechanical ventilation after the process that initiated the need for this support has improved and the patient is physiologically and psychologically well prepared (Table 10-7). It is now generally recommended that a brief daily trial of spontaneous breathing with low-level support be undertaken in patients whose acute need for ventilation has apparently resolved. If the result is satisfactory, a longer (30- to 120-minute) period of unsupported breathing should be observed before an extubation attempt. In such patients, “weaning” in the sense of graded accommodation to unassisted breathing using partial ventilatory support is usually unnecessary. Patients who fail to tolerate the “minimal support” trial require optimal preparation before another is undertaken (Table 10-8). The inability to discontinue mechanical support often results from failure to correct one or more of the factors that adversely affect strength, capacity for responding to stress, ventilatory requirement, gas exchange, cardiovascular function, or lung mechanics. Significant physiologic problems (infection, renal failure) should not be developing or worsening. The well-prepared patient is in appropriate electrolyte, pH, and fluid balance. Magnesium, potassium, calcium, and phosphate concentrations should be checked especially closely. Infection, arrhythmias, cardiac ischemia, and heart failure must be well controlled. Airways should be dilated optimally and kept as clear of retained secretions as possible (Fig. 10-4). Adequate sleep and nutritional support are essential. Excessive steroid doses should be avoided (Table 10-9).

### Table 10-7. Preparation for Weaning

- Encourage sleep; use hypnotics to complement sedation
- Daily wake-up during full support phase of ventilation
Early conversion to short-acting sedatives
- Dexmedetomidine
- Propofol
- Intermittent versed (midazolam)

Relieve discomfort—skeletal and visceral (bowel, bladder)
- Opiates relieve pain and improve depth of breathing ($\downarrow f/V_T$)

Reestablish “baseline” fluid balance
- Consider adding thiazide to loop diuretic
- Consider hemofiltration in refractory cases

Address cardiac issues—ischemia, rhythm, CHF

$R_x$ infection, secretions, pleural effusions, anemia

Table 10-8. Preparations for Weaning in Difficult Cases

1. Consider Depakote, quetiapine (Seroquel), risperidone, olanzapine (Zyprexa), for delirious or combative patients
2. Consider antiarrhythmic and ischemia prophylaxis
3. Consider trial of methylphenidate (Ritalin), modafinil (Provigil), for patients slow to awaken
4. Inspect the airway for retained mucus

Patients who are grossly fluid overloaded are often hypoalbuminemic and may not be easy to diurese. Partial repair of the albumin deficit, combined with a furosemide drip (and supplemented by chlorothiazide when necessary), can reduce the excess and greatly improve the chances for independent breathing. Continuous hemofiltration (again in conjunction with albumin, if indicated) is an excellent option to gently but efficiently eliminate tissue water for those whose kidney function is impaired and/or in whom diuresis is poorly tolerated or ineffective.
Figure 10-4. Airway pressure and flow waveforms generated in a patient with retained central airway secretions. Note the highly irregular expiratory flow and inspiratory pressure profiles (right) compared with normal (left). Such a patient may improve airflow and reduce the work of breathing impressively once the secretions are cleared.

Table 10-9. Therapeutic Measures to Enhance Weaning Progress

<table>
<thead>
<tr>
<th>Problem</th>
<th>Hypoxemia</th>
<th>Impaired Respiratory Mechanics</th>
<th>$\uparrow [V \text{ with dot above}]_E$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positioning</td>
<td>Positioning</td>
<td>Sedation</td>
<td></td>
</tr>
<tr>
<td>$\downarrow$ Secretions</td>
<td>$\uparrow$ Secretion clearance</td>
<td>$\downarrow$ Fever</td>
<td></td>
</tr>
<tr>
<td>Bronchodilation</td>
<td>Bronchodilation</td>
<td>$\downarrow$ Pain</td>
<td></td>
</tr>
<tr>
<td>Diuresis</td>
<td>Diuresis</td>
<td>$\downarrow V_D/V_T$</td>
<td></td>
</tr>
<tr>
<td>CPAP</td>
<td>Relieve cardiac ischemia Address congestive heart failure</td>
<td>Correct acidosis</td>
<td></td>
</tr>
<tr>
<td>$\uparrow$ FiO$_2$</td>
<td>$\downarrow [V \text{ with dot above}]_E$</td>
<td>Allow $\uparrow$ PaCO$_2$</td>
<td></td>
</tr>
</tbody>
</table>
Breathing circuit resistance
Drain large pleural effusions

<table>
<thead>
<tr>
<th>Problem</th>
<th>↓ Drive</th>
<th>↓ Endurance</th>
<th>Psychological Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Nutrition</td>
<td>Rest periods</td>
<td></td>
<td>Offer reassurance</td>
</tr>
<tr>
<td>↓ Loading</td>
<td>Ensure sleep</td>
<td></td>
<td>Convey plan</td>
</tr>
<tr>
<td>↓ Alkalosis</td>
<td>Optimal positioning</td>
<td></td>
<td>Anxiolytics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Atypical antipsychotics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quetiapine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Olanzapine</td>
</tr>
<tr>
<td>↓ Sedatives</td>
<td>Correct electrolytes</td>
<td></td>
<td>Encourage activity</td>
</tr>
<tr>
<td>↑ Sleep</td>
<td>↑ Caloric intake</td>
<td>Ambulation/physical RX</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Physical rehabilitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Optimize heart function</td>
<td>Adjust steroid dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Address adrenal function</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Correct severe anemia (&lt;8 g/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relieve abdominal distention</td>
<td></td>
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</tr>
</tbody>
</table>

*Partial listing.*

↑, increased; ↓, decreased.

Importance of the Daily “Wake-Up”

Unfortunately, many patients require heavy sedative dosing in the first phase of illness, with unwanted lingering effects. After the rescue phase of treatment, conversion to intermittent “as needed only” sedation or daily interruption of sedative administration (particularly when infused) to the point at which the patient is nearly conscious for a brief period helps ensure that sedative drug accumulation will not delay progress. Psychotropic agents such as haloperidol or dexmedetomidine may be needed to combat delirium, avoid panic reactions, and secure cooperation without suppressing consciousness. For patients without organic cause who are very slow to recover consciousness because of lingering drug effects, a trial of an alerting agent such as modafinil (Provigil) may be cautiously administered, especially for whom no clear contraindication exists.

Distention of the abdomen must be relieved. The ET tube quite frequently is a source of upper airway discomfort or pain, and this may be addressed by repositioning, relief of circuit tubing traction, and rarely by topical spray anesthetics. Care should be taken not to ventilate patients with chronic CO\textsubscript{2} retention to an artificially reduced PaCO\textsubscript{2} before the spontaneous breathing attempt. If this should happen, the patient may not be able to maintain the lower PaCO\textsubscript{2} level during unaided breathing, allowing acute acidosis to develop. Indeed, allowing a higher
than usual PaCO\textsubscript{2} during the support phase may be appropriate, as already noted. The nursing staff should be advised as soon as the physician has decided that a weaning attempt will be undertaken (preferably the night before). Such warnings can prevent untoward administration of sedatives, nutrients, or procedures that interfere with the trial's success.

**Sequence of Ventilator Withdrawal**

**The ABCDE Bundle**

Awareness of the contributions of excessive sedation, delirium, and immobility to ventilator dependence led to influential studies that emphasize the need to assure appropriate neurocognitive status during attempts at liberation from mechanical ventilation. Awakening, Breathing assessment, Choice and dosing of sedatives, Delirium monitoring and treatment, and Early mobilization are collectively known by the easily remembered “ABCDE” bundle. Clearly, periodic awakening and testing of breathing status during the support phase reduce unnecessary delays in the process. Choosing sedation regimens that minimize benzodiazepine use should reduce the incidence of delirium, especially among older patients. Although its superiority is debated, intermittent dosing (as opposed to continuous infusion) is a good and less costly option after the first stabilization phase of care that may help to avoid inadvertent sedative excess. Awareness and prevention of delirium, a condition that increases ventilator days and increases morbidity, deserves focused attention and nursing priority. Early mobilization from bed rest after and even before extubation is believed to yield many benefits, apart from muscle conditioning and coordination, as discussed in Chapter 18.

**Progression Toward Extubation**

The steps in removing mechanical support from the well-prepared, stable but ventilator-dependent patient are as follows: (1) estimation of the likelihood of success (physical examination, “parameter” measurement, secretion load, and cough assessment); (2) a trial of spontaneous ventilation; (3) gradual withdrawal of ventilatory power (weaning) if the trial of spontaneous breathing is poorly tolerated; (4) for most patients, a brief period of observation with minimal pressure support or CPAP before extubation and/or removal of the ventilator; (5) evaluation of glottic tightness and upper airway patency by the cuff leak test (see earlier and Chapter 6); and (6) close postextubation follow-up, using NIV, where necessary.

**Trial of Spontaneous Breathing**

Protocols for liberation assessment (spontaneous breathing trials) are extremely helpful in expediting independent breathing and generally allow the evaluation to be safely conducted by respiratory therapists and nurses. The physician should be quickly available at short notice and notified of the trial results, especially if extubation is advised. A trial of breathing without inspiratory assistance is a brief but stringent test of the ability to sustain spontaneous ventilation. It is generally undertaken when clinical judgment and a 3- to 5-minute observation period of breathing with only minimal levels of pressure support and CPAP suggest the likelihood that the patient can breathe spontaneously without ventilator support. For these patients, a longer test period of breathing with minimal pressure support or CPAP (30 to 120 minutes, depending on the degree of concern) should be conducted. Passing this minimal support trial justifies evaluation for extubation; failing either the brief or extended trial indicates that the causes of respiratory failure have not sufficiently resolved and further support and/or more gradual adaptation are necessary. Should overt fatigue be inadvertently allowed, a new trial should not be conducted before the patient rests for a sufficient period (>4 hours), and in the meantime is placed on a comfortable mode of assisted breathing.

Such a trial of spontaneous breathing can be conducted either by the classic T-piece method or simply by allowing the patient to breathe through an efficient ventilator circuit. The latter approach allows tidal volume and
A frequency to be followed, keeps an apnea alarm in place, prevents infections related to frequent circuit breaks, and avoids time and financial costs associated with circuit manipulation. Although tube diameter and \( [V \text{ with dot above}] \) should be considered, using more than 7 cm H\(_2\)O of pressure support during the trial does not seem advisable because it may mislead the physician into a false sense of optimism. (Even a low level of pressure support may help a marginally compensated patient.)

**Conducting the Trial**

One reasonable method for conducting the trial is as follows:

1. Ideally, the initial trials should be undertaken in the morning when the patient is well rested and alert and a full complement of staff is available. This also allows retesting later in the day when the patient's condition may have improved further. If the patient is alert, explain the purpose of the procedure.

2. Place the patient in the sitting or semiupright position for maximal mechanical advantage. This is especially important in the very obese.

3. Unless PaO\(_2\) is high enough to provide a comfortable margin, increase FiO\(_2\) by at least 10%; desaturation may develop during spontaneous breathing.

4. Suction the airway and oropharynx.

5. Monitor heart rate, blood pressure, tidal volume, respiratory rate, O\(_2\) saturation, and level of comfort before starting and every few minutes for the first 20 minutes. Although seldom used, tidal capnometry may be a helpful adjunct, as a steadily rising end-expiratory PCO\(_2\) suggests decompensation. If the outcome is in doubt, arterial blood gases are analyzed.

6. If the patient seems to be doing well, continue. However, if there is any question of tolerance, resume mechanical ventilation immediately. Do not let the patient become fatigued or emotionally distressed.

7. Moderate disturbances of vital signs can be seen in successful trials. However, terminate the trial if the patient indicates intolerable dyspnea or if diastolic blood pressure falls or rises by more than 20 mm Hg, pulse rises or falls more than 30/min, respiratory rate increases by more than 10/min over the initial spontaneous value, arterial blood desaturates sharply, mental status deteriorates, or worrisome arrhythmias or signs of coronary ischemia develop.

Very prolonged trials of spontaneous breathing are discouraged for patients who have no continuing need for the airway itself. In general, the duration of the trial should parallel the duration of pretrial mechanical ventilation and vary inversely with the confidence of the physician in the extubation outcome. It should be noted that the first minutes to hours off the ventilator are often the most stressful because tidal volume and functional residual capacity (FRC) may decrease and changes occur in central vascular volume, respiratory work, and pattern of breathing. When the patient has sustained spontaneous ventilation comfortably for 30 minutes to 2 hours, acute deterioration is less likely, and extubation should be considered if no contraindication exists, breathing pattern is stable, and the patient seems to be strong. Preparations for NIV or high-flow nasal cannula in the immediate postextubation period should be made for the high-risk patient with cardiac insufficiency, massive obesity, or marginal weaning parameters. Special caution is indicated for patients who have undergone a prolonged period of ventilatory support. Patients with potentially unstable respiratory drive should be watched carefully before removing the tube.

An aerosol of racemic epinephrine and NIV or CPAP should be considered for the patient with postextubation stridor. (Although controversial, moderate-dose steroids also may be justified for up to 24 hours afterward.) A
nasopharyngeal airway inserted immediately postextubation may help to aspirate secretions from the retropharynx and trachea. The sitting position helps maintain lung volume and glottis patency. High-flow nasal cannula helps serve this function in patients with low requirements. Although alertness should be maintained, the patient must be kept as comfortable and free from anxiety as feasible. Despite all precautions, it is distressingly common for marginal patients to require reintubation 12 to 48 hours after extubation (e.g., because of fatigue, sleep deprivation, aspiration, or upper airway obstruction). Therefore, recently extubated patients must be watched very closely for signs of decompensation and not allowed to eat until adequate swallowing reflexes have been tested and confirmed. Nocturnal support with Bi-PAP should be strongly considered in marginal cases.

STRATEGIES AND METHODS TO PROMOTE VENTILATOR INDEPENDENCE

General Principles
The physiologic determinants of ventilator dependence are addressed by ensuring hemodynamic stability (absence of cardiac ischemia, minimal use of pressors), adequate oxygenation \((\text{PaO}_2/\text{FiO}_2 \text{ ratio} > 200, \text{PEEP} < 8 \text{ cm H}_2\text{O}, \text{and FiO}_2 < 0.5)\), and ability to initiate strong inspiratory efforts (Table 10-6). Forcing the patient to work continuously may cause fitful sleep that compromises the weaning effort. The patient must be kept fully informed of the management plan, and most patients should be given absolute authority to terminate the trial if and when they experience intolerable discomfort. Panic reactions must be avoided, especially in patients with COPD who experience a self-reinforcing cycle of dyspnea, hyperinflation, functionally compromised muscle function, and often, pulmonary congestion or chest pain during these episodes. Tracheostomy should be considered after several failed liberation attempts, particularly if rapid recovery of muscle strength is unlikely. Tracheostomy provides a more stable and comfortable airway than an ET tube, allows ambulation and mouth closure, improves secretion clearance, and decreases both ventilatory dead space and the work of breathing.

Priorities
Several principles apply to most patients. First, the added external work of breathing must be minimized. Second, adequate lung volume must be maintained to prevent atelectasis, secretion retention, dysfunctional breathing patterns, and inefficient gas exchange. Third, deep tidal inflations should occur periodically to encourage recruitment of marginal lung units.

Methods of Removing Ventilator Support
At the outset, it should be recognized that the need for any form of partial ventilatory support in the process of establishing ventilator independence prior to extubation has been seriously questioned. Strong advocates of this doctrine believe that no form of partial assistance is indicated and that a ventilator-dependent patient should be fully supported until their underlying ability to breathe spontaneously has returned. This viewpoint, although understandable based on the available clinical trial data collected in diverse patient samples, often conflicts with a logical approach to the care of the subset of problematic patients with neuromuscular debility, cardiovascular compromise, and severe airflow obstruction.
Weaning Teams and Weaning Protocols

The complexity of reestablishing independent breathing is reflected by the reported success of weaning protocols that codify the preparations, evaluation, implementation, and pace of efforts to discontinue ventilatory support. Trained respiratory care practitioners (RTs) who ultimately report to the attending physician can be empowered to make assessments and undertake appropriate changes within the boundaries of agreed protocols. One successful approach is to assign dedicated teams composed of nurses and RTs with physician oversight to the task of consistent protocol-driven evaluation and implementation of ventilator management for multiple patients under their purview. The demonstrated benefits of weaning teams and weaning protocols appear to contradict the aforementioned all or none philosophy of ventilator management, as they infer that the details of the withdrawal process are important to the outcome. Yet, whatever stance is taken regarding partial ventilatory support, simply formalizing and consistently implementing rules governing sedation, daily assessment of spontaneous breathing potential, and ventilator management appear worthwhile in accelerating the return to independent breathing.

For patients who fail their daily brief trial of unsupported breathing, three weaning methods have been in widespread use for decades: progressive T-piece trials, intermittent mandatory ventilation (IMV), and PSV (Fig. 10-5). Recent practice has shifted away from gradual withdrawal of the ventilator and toward conducting a spontaneous breathing test once or twice daily, with full support in between failed attempts. Gradual withdrawal of ventilator power does retain a place, however, for the patient settings already discussed.

Unsupported (T-piece) Weaning

Using the intermittent spontaneous breathing method (minimal CPAP and pressure support or T-piece), the duration of independent breathing is lengthened progressively according to patient tolerance. T-piece weaning provides stress periods punctuated by recovery periods of total rest. Traditionally, the patient is disconnected from the ventilator and is attached to a source of humidified conditioned gas for a brief interval. Failure to progress to the next longer interval mandates reinstitution of continuous ventilator support for 6 to 24 hours and a search for correctable problems. If the patient remains comfortable while breathing spontaneously for 30 to 120 minutes, shows no sign of hemodynamic instability or respiratory decompensation, and maintains acceptable blood gases, spontaneous breathing may continue, punctuated by episodic manual hyperinflation and airway...
suctioning when needed. The duration that a patient must be observed during T-piece breathing before the ventilator is entirely discontinued is a matter of clinical judgment but generally should be governed by the length of time the patient has received mechanical ventilation and the apparent tolerance to spontaneous breathing. This time-honored approach can be defended, based on current knowledge of fatigue and muscle reconditioning. Furthermore, the T-piece generally provides conditioned gas at a modest resistive work cost imposed by the ET tube. The main disadvantages of using a T-piece are that it requires significant staff time to implement and monitor, involves repeated disconnections and physical manipulation of the circuitry (encouraging infection, see Chapter 8), forgoes airstream monitoring, and fosters abrupt transitions on and off positive pressure. The latter can prove problematic for patients who must assume a high-impedance workload, for those who are anxiety prone, and for those with ischemic or congestive heart failure.

**CPAP as Ventilatory Assistance**

It is well known that PEEP and CPAP (>0 cm H₂O) can improve lung compliance for patients with atelectasis and lung edema. Auto-PEEP presents a significant threshold load to ventilation for patients with a critical limitation of expiratory airflow. CPAP helps to counterbalance auto-PEEP and reduce the ventilatory requirement. For weak patients with severe airflow obstruction, the addition of CPAP may cause tidal volume to increase, as pressure support and breathing efforts become more effective. For stronger patients, CPAP may be used as a counterspring against which expiratory muscles can store energy for release during the subsequent inspiration—the “work-sharing” phenomenon.

**Partial Ventilatory Support**

**Synchronized Intermittent Mandatory Ventilation**

Tapering SIMV is now used infrequently as a weaning mode, as better options are now available. During synchronized intermittent mandatory ventilation (SIMV), the machine provides a selected number of timed positive pressure cycles (volume cycled or pressure controlled) that support 0% to 100% of the total minute ventilation. A clinician-specified number of machine-supported breaths per minute are interspersed among spontaneous breaths in synchrony with patient triggering efforts (see Chapter 7). SIMV provides a method to gradually transfer the work of breathing from the machine to the patient without repeated manipulation of the circuit tubing, thereby reducing the potential for technical error and infection while saving nursing time. Offering a full range of partial ventilatory support is potentially advantageous for patients with congestive heart failure or obstructive lung disease who cannot withstand sudden increments in venous return or the work of breathing and for those who experience anxiety when machine support is withdrawn abruptly. SIMV can provide relatively large breaths at a guaranteed backup rate and, when used expertly, may allow the patient to retrain and strengthen long-rested muscles. Used improperly, however, SIMV can increase the work of breathing, prolong the weaning period unnecessarily, promote chronic “fatigue,” or, worse, endanger the patient. No study has shown a relative advantage for SIMV over other modes and strategies.

**Pressure Support Ventilation**

In the weaning process, PSV offers an attractive option as an alternative or supplement to SIMV. When inspiratory pressure is set high enough, PSV can provide near-total ventilatory support. At low levels, PSV provides enough of a pressure boost to overcome the inspiratory (but not expiratory) resistance of the ET tube. Each breath is aided by the ventilator to the pressure level set by the physician and is flow cycled by the patient’s ventilatory impedance or expiratory effort. Unlike SIMV delivered without pressure support, PSV lends some flexibility to the amount of power
available from the machine. The patient can adapt to decreasing PSV by increasing frequency, thereby taking maximal advantage of machine power. In some instances, it is only when PSV falls below some critical value that the patient is forced to work actively to maintain tidal volume ($V_T$). The ability of the patient to draw greater assistance from the ventilator when the need arises may be particularly important for patients with variable $V_E$ requirements, and therefore, PSV may be an especially helpful adjunct for spontaneous breaths during SIMV.

**FIGURE 10-6.** Airway pressure and flow profiles for patients with and without airflow obstruction receiving pressure support. Because inspiratory flow decelerates only slowly when the airway is obstructed, achieving the 25% peak flow off-switch criterion (solid arrow) would require an excessive inspiratory time. The patient actively stiffens the chest wall to initiate expiration, as reflected by the end-inspiratory blip in airway pressure (open arrow).

**POTENTIAL PROBLEMS OF PRESSURE SUPPORT VENTILATION**

Although valuable for overcoming ET tube resistance, in allowing breaths of variable character and in conferring some flexibility in response to changing power requirements, PSV is not the perfect mode for partial ventilatory support, especially in the earlier implementations of this modality. When providing a fixed rate of rise to a set target pressure, PSV does not tailor its pressure output to the changing character of patient effort. Poorly selected pressure targets may elicit discomfort because of a power mismatch, timing asynchrony, or inappropriate tidal volume. When the impedance to inflation is very high, flow may decelerate so quickly that the cycle terminates prematurely. Conversely, for patients with severe airflow obstruction or narrow ET tubes, airway pressurization may need active termination, as inspiratory flow may assume a very slowly decelerating profile (Fig. 10-6). The threshold between tolerance and intolerance to a decrease in PSV is often quite distinct. A difference of only a few cm H$_2$O per cycle may separate comfort from overt dyspnea. Furthermore, the level of support offered by PSV varies directly with the impedance to chest inflation. Therefore, patients with variable inflation impedance (e.g., those predisposed to accumulate secretions or who experience bronchospasm during
the weaning trial) are less than optimal candidates for its use. The development of auto-PEEP may partially or completely nullify the contribution of a fixed PSV to the inspired $V_T$.

**Comparison of SIMV and PSV**

At the very onset of the weaning process, SIMV and PSV both support all breathing cycles and provide virtually identical ventilatory assistance for the same tidal volume. Similarly, at the completion of weaning, the patient must eventually breathe without assistance. Unquestionably, however, there are differences in the way that these techniques reload the respiratory muscles as support is withdrawn (Fig. 10-7).

**Self-Adjusting Modes**

Certain modes more recently introduced to clinical practice (e.g., proportional assist ventilation [PAV] and neurally adjusted ventilatory assist [NAVA]) have the potential to overcome some of the drawbacks of PSV and SIMV (see Chapter 7). Both allow patient control over the assisting pressure waveform while allowing the physician to effectively set the strength of the "auxiliary mechanical muscle" they provide (Fig. 10-8). The proportion of the effort per breath supported by the machine is provider-set. Neither PAV+ nor NAVA have been designed with the intention of weaning, but when intelligently managed by the caregiver, both may facilitate that process. Other automated approaches, such as adaptive support ventilation (ASV) and SmartCare/PS, utilize breathing pattern and/or capnographic information to judge patient tolerance and adjust support accordingly (Fig. 10-9). In concept, both are well suited to hastening the weaning process when coupled to a power withdrawal algorithm. Although experience and supportive scientific data are limited, both of these modes make logical use of feedback data and in theory withdraw pressure assistance, notifying the clinician when a spontaneous breathing trial is indicated (Fig. 10-10).

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**FIGURE 10-7.** A: Rate of reloading of the respiratory musculature during weaning by SIMV and PSV. As breathing frequency is reduced from the assist/control (100%) level, the patient receiving SIMV tends to respond by accepting the ventilatory workload relatively early in the machine withdrawal process. By contrast, relatively strong patients tend to reload the musculature linearly as pressure support is reduced, whereas weak patients tend to defer acceptance of the burden until relatively late in the withdrawal process. B: Transpulmonary pressure during gradual withdrawal of pressure support ventilation (PSV) cycles early and late in the weaning process. PSV weak effort Early Higher PSV Less effort Later Lower PSV More effort.
sequence. Initially, modest patient efforts are accentuated to maintain requisite tidal volumes as PSV is withdrawn.

**FIGURE 10-8.** Comparison of pressure support and proportional assist to a range of inspiratory muscle efforts. Unlike pressure support ventilation (PSV), which maintains the same pressure target independent of patient effort, proportional assist ventilation (PAV) attempts to continuously synchronize with and mirror muscular effort during inflation, using information based on monitored flow and volume to satisfy the equation of motion of the respiratory system. (Modified from Magdy Younes.)

There is little question that an attractive potential exists for automated decision support and for perfecting the responsiveness of the ventilator-patient connection. Except in the most sophisticated critical care environments, intelligent automated regulation of ventilatory parameters would be most welcome, as caregivers vary with respect to their skills, diligence, time demands, and resources. Logistical problems are likely to worsen in the near future as the complexity of advanced level care incessantly increases and the availability of caregivers to provide care that is compatible with best practice comes under economic strain. With the introduction of automated, logic-driven weaning protocols, we appear now to be heading in the right direction. Delays caused by caregiver inattention to patient tolerance and progress clearly can be reduced for appropriate patient groups in under-resourced and
staffed environments. Moreover, certain published data indicate that such approaches may prevent delays in machine withdrawal or extubation for nonsurgical patients even in high level caregiving environments. To this point, however, none of these recently introduced modes (e.g., SmartCare, ASV) has been adequately vetted by extensive clinical use or have they been rigorously and consistently demonstrated to confer benefit over well-managed standard alternatives in speeding the transition to independent breathing (see Chapter 7).

FIGURE 10-9. Determining the levels of applied airway pressure and respiratory rate needed to optimally satisfy the targeted ventilatory pattern associated with a given minute ventilation (solid hyperbolic line). Such breathing pattern analysis, complemented by ventilation efficiency data from the expired capnogram, serves to regulate inspiratory pressure (Pinspi) level and back-up respiratory rate (RR) during automated weaning. The machine algorithm continually probes patient readiness to breathe without assistance by gradually reducing pressure support and observing the resulting pattern and capnography responses. When a low enough PSV level is reached, the caregivers are alerted that a spontaneous breathing trial may be indicated.
In summary, although minimization of unnecessary ventilator assistance is a laudable goal, currently implemented automated weaning paradigms leave something to be desired. The populations to which they are applicable are restricted, their inputs are selective and insufficiently integrated with hemodynamic data and are unable to address important underlying issues that give rise to distress, such as cardiovascular congestion, secretion retention, bronchospasm, and psychological factors. Moreover, physiologic trajectory (as opposed to snapshot evaluations of present status) is not prioritized, and by design, automated systems do not address important stages of the ventilator liberation process that relate to preparation and extubation. With attention to such limitations, future automated systems may eventually prove of major value as personnel resources are stretched thin. With inherent shortcomings left unaddressed, however, automated weaning cannot yet be considered a superior methodology for effective and safe care delivery to our most challenging patients—the relatively few who actually need to be weaned at all.

**Practical Points When Gradual Ventilator Withdrawal Is Indicated**

1. Enough CPAP (3 to 7 cm H₂O) is applied to compensate for positional volume losses and/or auto-PEEP, and enough PSV is used to overcome ET tube resistance, considering both tube resistance and minute ventilation. Adding some level of PSV also lends flexibility to the level of support the patient may draw from, even when SIMV is selected (see above).

2. The patient must not be allowed to encounter sustained dyspnea and must be supported adequately at night to allow restful sleep and avoid hypoxemia.

3. With the patient receiving sufficient PSV to comfortably breathe at frequency of less than 20 breaths/min and a tidal volume of approximately 6 to 8 mL/kg, pressure support is withdrawn in decrements of 2 to 4 cm H₂O, as tolerated. If tidal volume or SaO₂ is marginal, one or two deeper SIMV breaths per minute may be applied to

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**FIGURE 10-10. Pressure support and stage of recovery.** As the patient improves, the capacity to sustain the breathing effort builds, allowing pressure support to be successfully withdrawn.
help avert microatelectasis and triggering of reflex tachypnea.

Progression to the next decrement is allowed if the patient is not dyspneic, the breathing frequency does not exceed 30 breaths/min and tidal volume remains greater than approximately 5 mL/kg for more than 5 to 15 minutes. If minute ventilation does not fall and the patient appears comfortable, the spontaneous breathing trial may proceed even if the RSBI (f/V\text{T}) greater than 100.

**REMOVAL OF THE ENDOTRACHEAL TUBE**

The need for continued ET intubation should be assessed independently of the need for ventilation. Although virtually all patients have disordered swallowing transiently after extubation, those likely to have a persisting problem of airway protection after tube removal (e.g., deep coma) should not be extubated. Because airway protection reflexes (pharyngeal gag and laryngeal closure) are lost earlier than cough reflexes triggered deep within the airway, a patient who fails to cough vigorously on tracheal suctioning is not likely to protect the airway effectively when the tube is removed (Table 10-10). For patients with copious airway secretions and temporarily ineffective cough, the tube should be retained to facilitate suctioning. VC greater than 20 mL/kg, a cough-induced inspiratory capacity greater than 2 × V\text{T}, and vigorous expulsive efforts with or without tracheal stimulation (secretions coughed into the external circuit or directly to atmosphere during circuit disconnection) predict effective coughing after extubation. Less frequently assessed indicators of coughing adequacy include an MIP more negative than ~40 cm H\text{2}O, a measured peak expiratory flow greater than 160 L/min (normal: 360 to 1,000 L/min), and an expiratory pressure generated against an occluded airway greater than 60 cm H\text{2}O.

 Patients who have had a difficult intubation or who have been reintubated one or more times are at higher risk for glottic swelling and upper airway obstruction after extubation. All such patients should be extubated with appropriate contingency preparations made for immediate reintubation should distress develop precipitously after extubation (see Chapter 6). Assuming that appropriate evaluative tests for ventilation adequacy and glottic patency (deflated cuff “leak” test with high-level PEEP) have already been performed, the extubation procedure itself is straightforward. In preparation, enteral feedings should be stopped, preferably 1 hour beforehand, and if a nasogastric tube is in place, it should be connected briefly to suction to evacuate any pools of retained gastric fluid. If the gastric tube is to be removed, ideally it should be pulled prior to extubation, as the gastric tube is often displaced and coils in the pharynx during ET tube extraction. Inhaled bronchodilator is given 15 minutes before extubation in patients with underlying airflow obstruction. A source of supplemental O\text{2} is readied. The retropharyngeal space should be cleared of supraglottic secretions to the extent possible, and 100% oxygen is delivered in the few minutes immediately prior to tube extraction. It is good practice to elevate PEEP (15 cm H\text{2}O) immediately (approx. five breaths) prior to cuff deflation and to keep higher PEEP throughout the extraction process. (Not only does it help to inflate the lungs and to start the extraction from a relatively high lung volume but also flow from the tube tip propels secretions inaccessible to a suction catheter that remain above the cuff into the mouth for easy expectoration.) With the cuff deflated and PEEP applied, the patient is instructed to exhale forcefully as the tube is quickly removed and to cough vigorously immediately afterward. The appropriate concentration of O\text{2} is administered immediately by face mask or nasal prongs.

<table>
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<th>Table 10-10. Peri-extubation Care</th>
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<td><strong>PRE-EXTUBATION</strong></td>
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<td>• Aggressive secretion clearance, bronchodilators, and fluid balance</td>
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High PEEP immediately before and during tube extraction
Consider nasal trumpet preextubation
Bronchoscopic inspection of airway prior to extubation

POST-EXTUBATION
Humidified intermittent and nocturnal noninvasive ventilation (Bi-PAP)
Consider high-flow nasal catheter
Nasal prongs whenever possible

In a patient with a tracheostomy, the ability to phonate and expectorate with the tube cuff partially deflated (after oropharyngeal suctioning) is generally considered to be a positive predictive sign. Because compromise of coughing and swallowing in the postextubation period generally parallels the duration of translaryngeal intubation, particular attention should be paid to assiduous tracheobronchial hygiene in these cases. Suctioning, corticosteroids, bronchodilators, Bi-PAP or high-flow nasal oxygen, sitting position, antibiotics, and careful regulation of electrolyte, glucose, and cardiovascular status often make the difference between a patient who bridges the period of difficulty and another who must be reintubated.

AVOIDING DELAYED LIBERATION FAILURES AND REINTUBATION
The need for reintubation carries an adverse prognosis, perhaps partially accounted for by the patient's underlying condition and partially by the hazards of extended intubation/mechanical ventilation. The 24- to 48-hours period immediately after ventilator disconnection may be highly dynamic, as the larynx, the upper airway, and the swallowing mechanism may be seriously, but temporarily, dysfunctional. Nonetheless, the patient must readjust to spontaneous breathing and assume responsibility for airway secretion clearance. Stresses arising soon after extubation may result from cardiac ischemia, arrhythmia, pulmonary congestion, atelectasis, secretion retention, oropharyngeal aspiration, or temporary swelling of glottic and subglottic tissues. Appropriate pharmacoprophylaxis, upright positioning, and vigorous attempts to encourage deep breathing, coughing, and mobilization to chair are helpful. In lethargic patients, secretions may pool in the retropharynx and should be aspirated periodically via a nasopharyngeal airway (“trumpet”). Caution should be used when initiating oral feeding after lengthy intubation. Informal or formal swallowing studies are indicated depending on the clinician's degree of suspicion. Premature resumption of normal diet can be hazardous because temporary swallowing dysfunction and impaired glottic defenses are common, especially after prolonged intubation. Intermittent NIV and/or high-flow nasal cannula during this period may help as a bridge across the immediate postextubation period in challenging patients (see below). Anything that can be done to improve sleep quality (including NIV, fewer sleep interruptions, and relatively safe hypnotics, such as zolpidem) is worth implementing to avoid sleep deprivation and eventual exhaustion. The medication list should be reviewed, and the potential for either mental depression by scheduled narcotics or excessive mental stimulation by high-dose steroids and catecholamines minimized. Pulse oximetry, echocardiography, and electrocardiography are helpful monitors during this period as well.

Manually or mechanically assisted coughing may be helpful in reaching this threshold in the days that follow extubation.

The Persistently Ventilator-Dependent Patient
The need for continued ventilatory support is often psychological as well as physiological (Table 10-11).
A few points are important to keep in mind.
1. The patient must be “co-opted” into the weaning effort and kept fully advised of the treatment plan.

2. Most patients should be given full “veto” power to terminate an overly taxing trial.

3. “Panic” reactions are especially detrimental for patients with airflow obstruction. At such times, these patients generate increased volumes of CO$_2$ and experience poorly coordinated breathing, hyperinflation, hypoxemia, and extreme dyspnea.

4. A novel sedative and anxiolytic with little respiratory depression (dexmedetomidine) and psychotropic agents such as olanzapine, quetiapine, and Depakote may benefit selected patients who awake into agitated delirium when sedatives are withdrawn.

5. The patient must be fully rested. This can best be ensured by 10 to 12 hours of full ventilatory support and a good night of sleep before the attempt.

6. Hidden problems such as diastolic dysfunction, coronary insufficiency, endocrinopathy (hypoadrenalism, hypothyroidism), subtle strokes, critical illness polyneuropathy, steroid myopathy, paralytic neuromyopathy, or Parkinson disease may explain protracted ventilator dependence and must be sought aggressively in puzzling cases. Large pleural effusions must be drained, and the stomach must be decompressed.

### Table 10-11. Aids to Wean the Unweanable Patient

| Co-opt the patient into the process |
| Confer veto power to the patient   |
| Avoid panic reactions             |
| Consider nonsedating anxiolytics (e.g., dexmedetomidine)/psychotropics |
| Rest fully before trial/ensure adequate restful sleep |
| Check for “hidden” cardiovascular and endocrine problems |
| Mobilize and exercise to the extent possible |
| Respiratory muscle training       |

7. Mobilization aids in general rehabilitation and is often the key to the weaning effort. Prolonged bed rest is attended by multiple adverse physiologic changes related to the changed vector of gravitational forces, including depressed vascular tone, reduced extravascular volume, loss of red cell mass, electrolyte shifts, calcium depletion, aberrations of hormonal balance, and depletion of skeletal muscle mass (see Chapter 18). Prevented from weight bearing, the lower extremities undergo disproportionate atrophy in patients continually at bed rest. Performing arm and leg exercises in bed, periodic transfers to chair, and (in tracheostomized patients) even ambulation aid greatly in the rehabilitation effort. Chronically ventilator-dependent patients demand less nursing attention than other ICU patients. Immobilized and deprived of sensory stimulation, they often become passive, discouraged, or poorly cooperative. Efforts to provide sensory input; to restore the natural diurnal rhythms of light, activity, and noise, normal activities, social interactions; and to provide physical and occupational therapy may improve mental outlook, strength, and prospects for recovery (Fig. 10-11).

**Muscle Training**

As soon as the crisis period has passed, it makes good physiologic sense to deliberately stress the ventilatory musculature for brief periods several times daily, encouraging spontaneous breathing (CPAP with low-level PSV). After being fully rested, such “wind sprints” may help strengthen, recoordinate, and condition the
ventilatory muscles in a fashion similar to athletic training for limb muscles. Many patients with good strength but a tendency to panic do best when extubated directly rather than being tapered to low levels of machine support. This is particularly true when a highly resistive ET tube is in place (e.g., a small-caliber nasal tube).

The decision to extubate despite a failed spontaneous breathing trial is encouraged by noting that minute ventilation falls significantly during sleep, rises during the spontaneous breathing trial, and that the breathing pattern is highly variable. Those who cannot be extubated may benefit from tracheostomy, a procedure that lowers airway resistance and apparatus dead space, improves secretion hygiene, and allows mobilization.

**FIGURE 10-11. Exercise while receiving mechanical ventilation.** Cycling in bed (A) and ambulation (B).

For a patient whose primary problem is ventilatory mechanics (and not respiratory drive), it may be worthwhile to allow PaCO\(_2\) to rise slowly over several days while maintaining acceptable oxygenation and pH balance. Higher PaCO\(_2\) enables each breath to eliminate CO\(_2\) more efficiently. Special attention should be paid to repairing any bicarbonate deficit, which often results from saline administration, diarrhea, or renal tubular dysfunction. Higher bicarbonate levels buffer fluctuations in PaCO\(_2\) more effectively and reduce dyspnea.

**Noninvasive Ventilation as a Bridge to Ventilator Independence**

Over the past decade, the development of appropriate equipment and comfortable interfaces has encouraged the meteoric growth of NIV in a variety of acute applications (see Chapter 7). In the postextubation period, the provision of ventilatory support may maintain upper airway patency and improve sleep quality. Periodic rest may keep the weak patient from the verge of fatigue. COPD patients appear to benefit the most from NIV in the postextubation period. Care must be taken to assure adequate hydration of the inspired airstream, which tends to be dry, increased in quantity, and inhaled through the mouth. If the NIV is unhumidified, secretion thickening in the oropharynx and airway poses a serious risk for retention that may precipitate ventilatory failure and need for reintubation. Well-conditioned high-flow nasal oxygen is an excellent option for many patients who need minimal ventilatory assistance, as it leaves the mouth unencumbered, hydrates the gas flow, provides low level CPAP, and improves the efficiency of ventilation (see Chapter 7).

**Tracheostomy**

Timing for tracheostomy must be considered on an individual basis. Some patients persisting in ventilatory failure (e.g., those with slowly reversible or irreversible neurological problems or upper respiratory pathology) should receive early tracheostomy. For patients with acute lung disorders that are expected to reverse, there is no ironclad rule regarding when tracheostomy should be performed. Routine early tracheostomy may facilitate
transfer out of the ICU but holds no consistent long-term outcome advantage for lung health and poses some problems of its own. As a guideline, tracheostomy may be appropriate anytime after the first 7 to 10 days. The decision to undertake tracheostomy should consider the pace of improvement; if the patient is progressing sufficiently to be ready for extubation within 3 to 5 days, tracheostomy can be deferred reasonably. Patients who have demonstrated the need to be reintubated without readily correctable cause merit consideration. It should be emphasized, however, that for some patients who are making slow progress—particularly those who do not fight ventilation—ET tubes may be kept in place for longer than 3 weeks without permanent laryngeal or tracheal injury or need for tracheostomy.

**Importance of Communication**

Intubated patients who require ventilatory support often are frustrated in their attempts to communicate with their families, friends, and caregivers. The psychological value of establishing a reliable means of communication frequently is underestimated. Writing pads and letter, “pick-choice” message boards, and image cards are commonly used for endotracheally intubated patients but are cumbersome at best. For the tracheostomy patient, however, better options are available. Effective devices for communication after tracheostomy include vibrators placed over the larynx or cheek and for those strong enough to breathe spontaneously, oneway inspiratory valves (Passy Muir valves). Although specialized tubes that direct a manually gated gas flow through the vocal cords are available, a simpler approach for any trached and ventilated patient is to deflate the cuff with 10 cm H₂O of PEEP applied. The ventilator's attempt to maintain pressure will result in flow around the trach tube and across the cords, allowing crude phonation.

**Weaning from Tracheostomy**

Consideration should be given to removing the tracheostomy tube when the patient no longer requires suctioning for secretion removal, high fractions of inspired oxygen, or periodic reconnection to the ventilator. Replacement of the standard tracheostomy tube with a fenestrated one with inner cannula narrows the lumen somewhat facilitates talking and allows easier assessment of true cough effectiveness. The predictors of coughing ability were discussed earlier. There are essentially three methods for gradually discontinuing a tracheostomy: use of partial plugs, use of progressively smaller tracheostomy tubes, and use of stomal “buttons.” Plugs that progressively occlude a standard-sized tracheostomy orifice (e.g., one-half to three-quarters plugs) can be used to assess the need for continued intubation. (The cuff on the ET tube must be deflated during orifice occlusion.) However, it should be remembered that an occluded tracheostomy tube severely narrows the effective tracheal lumen, thereby increasing the work of breathing and the tendency toward secretion retention. For this reason, many physicians prefer to replace the original tracheostomy with progressively smaller uncuffed (or uninflated) tracheal cannulae, such as silver Jackson tubes. Unfortunately, the stomal orifice rapidly adapts to the smaller-caliber tube as well, so that effective ventilation through the tracheostomy might not be possible if an acute need arises. If the ability to sustain spontaneous ventilation, clear secretions, or protect the airway remains questionable, a well-fitted and snug tracheostomy “button” will maintain the stoma over several days to weeks to allow tube reinsertion, noninvasive nasal or mask ventilation, emergency ventilation, suctioning, and effective administration of inhaled bronchodilators without adding substantially to airway resistance. NIV often aids in providing adequate nocturnal ventilatory assistance, as well as the power necessary to bridge the period of adaptation that follows decannulation.

For certain difficult patients (e.g., those with debilitating weakness, paralysis, or neuromuscular disease), a vigorous program of assisted coughing may be instrumental in achieving airway clearance. This may involve the application of high inflation volumes followed by abdominal thrusts timed to coincide with glottic opening. For patients who cannot maintain glottic closure or for whom abdominal compression is compromised by thoracic
cage deformity or extreme obesity, deep spontaneous inspiration and manual abdominal compression may be ineffective; here, a commercially available “insufflation/exsufflation” device (capable of transiently generating 50 cm H₂O of positive and negative pressures when applied to the face mask or ET tube) may be especially useful. A vibratory vest or pulsating nebulizer “MetaNeb” may enhance secretion removal in weakened patients with copious airway secretion who do not respond to other measures (e.g., antibiotics, steroids). For patients with severe obstructive airway disease, however, assisted coughing techniques may be fruitless.

**SUGGESTED READINGS**


Chapter 11

Intensive Care Unit Imaging

Andrew Hartigan MD

Co-written with

• Key Points

1. The value of a portable CXR usually depends upon obtaining an appropriately penetrated, upright exposure in full inspiration. Consistency of technique from day to day is essential to optimize the value of films.

2. Parenchymal infiltrates have many common potential etiologies (including atelectasis, embolism, edema, and hemorrhage). Only a small minority of infiltrates represents infection; the diagnosis of nosocomial pneumonia requires clinical correlation and microbiologic confirmation.

3. Although certain signs may be highly suggestive, the CXR does not reliably distinguish the high-permeability edema of ARDS from the hydrostatic pulmonary edema of volume overload or left heart failure.

4. Ultrasound has burgeoned as an imaging modality for applications by the intensivist, as it poses no risk of contrast or radiation exposure, can provide definitive, dynamic, and high-value information. With its near-immediate availability, ultrasound can facilitate an expanding variety of percutaneous bedside procedures and answer emergent questions relating to effusion, lung edema, and pneumothorax.

5. Chest CT is quickly completed and often reveals conditions that were not suspected by plain radiographs. Reconstructed images sharply and convincingly define pathoanatomy, especially when contrast agents can be safely given.

6. CT is the single best imaging modality for evaluating the abdomen unless the primary working diagnosis is cholelithiasis, ureteral obstruction, or ectopic pregnancy. Ultrasound may be equally informative in such cases and is often the better choice when contrast exposure for CT is contraindicated.

7. Assuming the availability of CT scanning, magnetic resonance imaging (MRI), a modality that provides superb soft tissue imaging without ionizing radiation exposure is but is time consuming and has relatively few ICU applications that do not relate to neurocritical care.

8. Early interactive consultation with the diagnostic or interventional radiologist usually assures the best selection of procedure, optimal patient preparation, and efficient, bundled sequencing of tests and interventions.

OVERVIEW OF RECENT ADVANCES IN ICU IMAGING

Conventional and specialized imaging techniques are vital to the care of the critically ill. Diagnostically, computed tomographic (CT) scanning and magnetic resonance imaging (MRI) are indispensable for neurologic, chest, abdominal, and sinus evaluations. Ultrasound (US) facilitates cardiac, vascular, renal, gallbladder, pleural, and lung assessment, and though sparingly used, nuclear medicine techniques sometimes help in confirming embolic disease, gastrointestinal (GI) bleeding, and fistulous communications. Bedside availability of US has made thoracentesis and central venous catheter (CVC) placement safer and easier. Interventional radiology assumes an ever-increasing role in performing repairs that once could only be addressed surgically. This ever-increasing
list includes embolization of cerebral aneurysms, percutaneous aortic aneurysm grafting, embolization of life-threatening bleeding vessels, placement of intravascular filters, emergent stroke intervention, and pulmonary embolism (PE) lysis. These and other specialized applications are discussed here and elsewhere in this volume in conjunction with the specific diseases they help define. This chapter concentrates on imaging applications relevant to the critical care setting: the chest X-ray (CXR) and chest CT, the abdominal plain film, ICU ultrasound, and interventional procedures.

Major advances have occurred in ICU radiology over the last two decades as technological progress has perfected digital filming techniques, accelerated acquisition and processing speeds, deployed ultrasonography to the bedside, and dramatically enabled improved imaging communications to and from the ICU point of care. Clinical data and background information can be rapidly reviewed by both clinician and radiologist, and digital images can now be viewed remotely on almost any computer, portable X-ray machine, or handheld electronic device. This technological revolution has brought a host of improvements. Among them:

1. “Hard copy” films are no longer lost or out of chronological order.
2. Delays in availability have decreased.
3. It is now possible to manipulate image brightness and contrast and to compare new images side-by-side with previous ones.
4. Geographically separated physicians can simultaneously view a study.
5. Physicians no longer need to leave the ICU to view studies.

There are two important disadvantages of the digital revolution. First, although the situation is rapidly improving, the expensive high-resolution displays necessary to see the smallest details are not widely available; hence, studies are often examined on suboptimal screens. Second, the frequent meetings of the intensivist with radiologist that nearly always occurred when hard copy X-ray films were used have all but vanished. Although “throughput” efficiency may be enhanced, such isolation is unquestionably detrimental. Failure to connect face-to-face often deprives the radiologist of important clinical information to aid in effective consultation, may result in clinicians overlooking subtle but important findings, and eliminates a valuable educational function.

CHEST RADIOGRAPHY

Technique

Although the CT has displaced the bedside film from its former diagnostic prominence, the simple portable film suffices to answer many questions that require repeated follow up and do not require CT precision. Bedside radiography, therefore, retains a strong place for many applications. However, the usefulness of the portable anterior-posterior (AP) CXR is largely determined by positioning and exposure technique. One simple measure to improve the ability to interpret CXRs is to reposition overlying devices (e.g., ECG monitoring wires, ventilator and IV tubing, external pacing pads, and nasogastric or orogastric tubes) out of the field of the radiograph. Orientation of the patient with respect to the radiographic beam is of critical importance. Kyphotic, lordotic, and rotated projections impact the apparent dimensions of intrathoracic structures and detection of pathology. The use of “gravity-dependent” radiopaque markers on the corners of portable films helps clarify a patient's position. The AP technique blurs and magnifies the anterior mediastinum and great vessels, in some cases by as much as 20%. Obese patients present particular challenges in separating what is normal from what is not, especially when filmed supine (Fig. 11-1). Moreover, apart from the AP requirement itself, radiographs obtained in supine patients exaggerate apparent cardiovascular dimensions because of augmented venous filling, higher diaphragms, and reduced lung volume. For example, the azygous vein distends in the supine normal subject but
collapses in the upright position (Fig. 11-2). Conversely, supine films often render imperceptible a small pneumothorax or pleural effusion. Rotation produces artifactual hemidiaphragm elevations and depressions. In diffuse infiltrative processes, lateral positioning accentuates asymmetry—making the dependent lung appear more affected. Film penetration may emphasize or diminish parenchymal lung markings. Consistency in exposure technique is critical to allow day-to-day comparison of radiographs. A properly exposed CXR should reveal vertebral interspaces in the retrocardiac region. Films on which these interspaces are not visualized are underpenetrated, exaggerating parenchymal markings and making visualization of any air bronchograms more difficult.

Changes in lung volume influence the appearance of parenchymal infiltrates, especially in mechanically ventilated patients and in those receiving positive end-expiratory pressure (PEEP). Infiltrates seen on a CXR obtained in full inspiration on the ventilator usually appear less dense than when viewed in partial inspiration. Similarly, many patients will have a “less-infiltrated” appearing CXR following the application of higher PEEP. Unfortunately, there is no predictable relationship between the level of PEEP applied and its impact on the appearance of the film. To facilitate comparison, therefore, serial films ideally should be exposed with the patient in the same position, during the same phase of the respiratory cycle, and with comparable tidal volume and end-expiratory pressure. (Clearly, such an ideal for interpretation may not be feasible or clinically advisable, but such influences should be borne in mind.) Infusions of large volumes of fluids, the development of oliguria, or superimposed myocardial dysfunction produce a rapidly deteriorating radiographic picture. Bronchoalveolar lavage may cause the appearance of localized infiltrates because of residual lavage fluid and atelectasis. Bedside lung US for lung and pleural interrogation by the ICU provider has the potential to obviate the need for repeated radiation exposure to resolve diagnostic questions or track progress.

**FIGURE 11-1. Left:** Normal posterior-anterior (PA) upright chest radiograph. Note the definition and dimensions of the heart and vascular structures. **Right:** Supine AP chest radiograph in massively obese normal subject. Note the widened mediastinum, enlarged heart shadow, and symmetrically elevated hemidiaphragms.
FIGURE 11-2. Distention of azygos vein, indicating higher than normal pressures in the SVC, is seen on frontal chest film as a circular or lenticular shadow (arrow) at its point of anatomic insertion.

Film Timing

Because of the high likelihood of finding significant abnormalities (e.g., tube malposition, pneumothorax), it is worthwhile to obtain a CXR on almost all patients upon arrival in the ICU. The frequency with which radiographs are necessary after stabilization is much more controversial. General agreement exists that CXRs should be obtained promptly after invasive procedures such as endotracheal (ET) intubation, feeding tube placement, transvenous pacemaker insertion, thoracentesis, pleural biopsy, and central vascular catheter placement to ensure proper tube or catheter position and exclude complications. Likewise, a film should probably be obtained routinely after transbronchial biopsy, although the need for such a study in the nonintubated patient is debated. In all but emergency situations, a CXR should follow failed attempts at catheterization via the subclavian route before contralateral placement is attempted.

Although many ICUs continue to routinely obtain daily or even more frequent radiographs in patients with cardiopulmonary disease or dysfunction, regularly scheduled films are not necessary in all patients. Despite data indicating that a quarter to two thirds of routine ICU CXRs demonstrate an abnormality or minor change, many of these findings are nonacute or inconsequential. Most important developments are signaled by clinically suggestive signs or careful examination of the patient before obtaining the radiograph. Prospective study indicates that fewer than 10% of films demonstrate a new significant finding, and only a fraction of these are not anticipated by clinical examination. A reasonable compromise position is to obtain daily “routine” radiographs on mechanically ventilated patients who have hemodynamic or respiratory instability. The need for additional films should be dictated by changes in the patient’s clinical condition and by the performance of procedures. In the stable, mechanically ventilated patient, especially those with a tracheostomy, studies can safely be obtained less frequently. Obviously, deterioration should prompt reevaluation.
FIGURE 11-3. Location of the main carina on the frontal film. The separation between the right and left main bronchi (arrow) almost invariably occurs at the level of the 6 and 7 posterior ribs, directionally “southwest” of the aortic knob.

Placement of Tubes and Catheters

Tracheal Tube Position

Because up to 25% of ET tubes are initially positioned suboptimally, radiographic confirmation of tube location is crucial; positioning the ET tube in the right main bronchus often results in right upper lobe or left lung atelectasis. (Left main intubations are uncommon because the left main bronchus is smaller and angulates sharply from the tracheal axis.) Conversely, if the tube tip lies too high in the trachea (above the level of the clavicles), unintended extubation is likely. When the head is in a neutral position, the tip of the ET tube should rest in the midtrachea, approximately 5 cm above the carina. In adult patients, the T6 vertebral level is a good estimate of carinal position if it cannot be directly visualized (Fig. 11-3). The carina is usually located just inferior to the level of the aortic arch. (Another method to locate an unseen carina uses the intersection of the midline of the trachea with a 45-degree bisecting line, which passes through the middle of the aortic knob.) ET tubes move with flexion, extension, and rotation of the neck. Contrary to what might be expected, the tube tip moves caudally when the neck is flexed (i.e., chin down = tip down). Conversely, head rotation away from the midline and neck extension elevates the ET tube tip. Total tip excursion may be as much as 4 cm.

The normal ET or tracheostomy tube should occupy one half to two thirds of the tracheal width and should not cause bulging of the trachea in the region of the tube cuff. Bulging is associated with an increased risk of subsequent airway stenosis, presumably the result of tracheal wall ischemia from cuff overinflation. Gradual dilation of the trachea may occur during long-term positive pressure ventilation, but every effort should be made
to prevent this complication by minimizing both ventilator cycling pressure and cuff sealing pressures.

After tracheostomy, a CXR may detect subcutaneous air, pneumothorax, pneumomediastinum, or malposition of the tube. The T3 vertebral level defines the ideal position of the tracheostomy site. (This usually places the tip halfway between the stoma and the carina.) Unlike the orally placed ET tube, the tracheostomy tube does not change position with neck flexion or extension. Lateral radiographs are necessary for evaluation of anteroposterior angulation. Sharp anterior angulation of the tracheal tube is associated with the development of tracheoinnominate fistulas, whereas continued posterior angulation risks erosion and tracheoesophageal fistula. Massive hemoptysis usually signals the former condition, whereas sudden massive gastric distention with air occurs in the latter. Fortunately, both complications are quite rare in modern practice.

In patients with previous intubation or tracheostomy, the tracheal air column should be examined for evidence of stenosis. Tracheal narrowing is relatively common and can occur at the level of the tracheal tube tip, at the cuff, or at the tracheostomy tube stoma (most common site). The typical hourglass-shaped narrowing can be hard to visualize on a single AP radiograph, and stenosis must be substantial (luminal opening <4 mm) to be symptomatic. CT establishes a definitive diagnosis.

Central Venous Catheters
For accurate pressure measurement, the tip of the CVC should lie within the thorax, well beyond any venous valves. These valves are typically located in the subclavian and jugular veins, approximately 2.5 cm from their junctions with the brachiocephalic trunk (at the radiographic level of the anterior first rib). Because CVC catheters in the right atrium or ventricle may cause arrhythmias or perforation, the desirable location for these lines is in the midsuperior vena cava, with the tip directed inferiorly. Radiographically, catheter tips positioned above the superior margin of the right mainstem bronchus are unlikely to rest in the atrium. Catheters should have no sharp bends along their course and should descend lateral and parallel to the spine. Stiff catheters, particularly hemodialysis lines inserted through the left subclavian vein may impinge on the lateral wall of superior vena cava, potentially resulting in vascular perforation. Complications resulting from vascular puncture include air embolism, fluid infusion into the pericardium or pleural space, hemopneumothorax, and pericardial tamponade. Imaging studies reveal that partial thrombosis occurs distressingly often with CVCs and peripherally inserted central catheters (PICC lines). Postprocedure radiographs reveal complications in up to 15% of CVC placements. On occasion, catheters inserted via the subclavian route can pass across the midline into the contralateral subclavian vein, or even turn cephalad entering the internal jugular veins. Similarly, catheters inserted in the internal jugular veins may track into the subclavian vein of either side. The phenomenon of a subclavian catheter crossing the midline is most common when a triple-lumen catheter is threaded through a larger bore channel already in placed in the right subclavian vein. Many clinicians are comfortable leaving CVCs, which terminate in the contralateral subclavian in place, provided there are no clinical effects but are less at ease with CVCs terminating in the internal jugular vein.

As a general rule, it is a good idea to obtain a CXR following failed attempts at CVC placement before attempting insertion on the contralateral side. Doing so reduces the already tiny chance of producing bilateral pneumothoraces. Obviously, this safeguard must be abandoned under truly emergent circumstances where venous access must be obtained immediately.

Pulmonary Artery (Swan-Ganz) Catheter
Every insertion-related complication of CVCs, including pneumothorax, pleural entry, and arterial injury, can result from the placement of the pulmonary artery catheter (PAC) as well. Unique complications of PAC placement include knotting or looping and entanglement with other catheters or pacing wires and pulmonary artery rupture and infarction. Knotting or
entanglement of PACs with other catheters is a frightening prospect but can usually be avoided and need not be dangerous if a few simple steps are followed. Knotting can largely be avoided by not advancing the catheter more than 20 cm before the next chamber’s pressure tracing is observed. For example, a right ventricular tracing should be seen with less than 20 cm of catheter advancement after obtaining a right atrial pressure tracing, and a pulmonary artery tracing should be obtained before another 20 cm is advanced after first obtaining the right ventricular tracing. Doing so prevents the catheter from forming a large loop in the right atrium or ventricle. If the PAC does become knotted or entangled with another device (e.g., pacing wire or vena caval filter), it is essential to resist the temptation to pull on the catheter harder to extract it; doing so only tightens the knot, making eventual extraction more difficult. Almost always, knotted catheters can be “untied” under fluoroscopic guidance by an interventional radiologist simply by loosening the knot, with aid of a stiff internal guidewire.

Unrelieved pulmonary arterial blockage has been a reported complication in 1% to 10% of PAC placements. The most common radiographic finding is distal catheter tip migration, with or without pulmonary infarction. With an uninflated balloon, the tip of the PAC ideally overlies the middle third of a well-centered AP CXR (within 5 cm of the midline). Distal migration is common in the first hours after insertion as the catheter softens and is propelled distally by repeated right ventricular contractions. If pressure tracings suggest continuous wedging, it is important to look for distal migration, as well as a catheter folded on itself across the pulmonic valve or a persistently inflated balloon (appearing as a 1-cm diameter, rounded lucency at the tip of the catheter). Inflating the balloon of an inappropriately distal PAC can result in immediate catastrophic pulmonary artery rupture or delayed formation of a pulmonary artery pseudoaneurysm. Pseudoaneurysms present as indistinct rounded densities on CXR 1 to 3 weeks after PAC placement. The diagnosis is easily confirmed by MRI or contrasted chest CT.

The width of the mediastinal and cardiac shadows should be assessed following placement of PACs and CVCs, because perforation of the free wall of the right ventricle (fortunately, rare) has the potential to result in pericardial tamponade.

**Pacing Wires**

When transvenous pacing wires are inserted emergently, they often lie malpositioned in the coronary sinus, right atrium, or pulmonary artery outflow tract. On an AP view of the chest, a properly placed pacing catheter should have a gentle curve with the tip overlying the shadow of the right ventricular apex. However, it is often difficult to assess the position of the pacing wire on a single film. On a lateral view, the tip of the catheter should lie within 4 mm of the epicardial fat stripe and point anteriorly. (Posterior angulation suggests coronary sinus placement.) In patients with permanent pacemakers, leads commonly fracture at the entrance to the pulse generator, a site that should be checked routinely. Pacing wires can also result in cardiac perforation, so it is important to examine the CXR for signs of tamponade and if suspicion is sufficient, perform bedside cardiac US.

**Chest Tubes**

The optimal position for a chest tube depends on the reason for its placement. Posterior positioning is ideal for the drainage of free-flowing pleural fluid, whereas anterosuperior placement is preferred for air removal. On an AP chest film, posteriorly placed tubes are closer to the film than those placed anteriorly. This proximity of the chest tube to the film results in a “sharp” or focused appearance of the catheter edge and its radiopaque stripe. Conversely, anteriorly placed chest tubes often have fuzzy or blurred margins. Chest tube location may appear appropriate on a single AP film, even though the tube actually lies within subcutaneous tissues or lung parenchyma. Unexpected failure to re-expand the pneumothorax or drain the effusion should be a clue to extrapleural placement. A chest CT may be necessary to confirm appropriate positioning. On plain film, another clue to the extrapleural location of a chest tube is the inability to visualize both sides of the catheter. Larger chest tubes are constructed with a “sentinel eye,” an interruption of the longitudinal radiopaque stripe that delineates the opening of the chest tube closest to the drainage apparatus. This hole must lie within the pleural space to
achieve adequate drainage and ensure that no air enters the tube via the subcutaneous tissue. After removal of
a larger chest tube, fibrinous thickening may produce a persisting tube track, which mimics the visceral pleural
boundary, suggesting pneumothorax.

**Intra-aortic Balloon**

The intra-aortic balloon (IAB) is an inflatable device placed in the proximal aorta to assist the failing ventricle.
Diastolic inflation of the balloon produces a distinct, rounded lucency within the aortic shadow, but in systole, the
deflated balloon is not visible (whereas the supporting catheter is). Ideal positioning places the catheter tip just
distal to the left subclavian artery. Placed too cephalad, the IAB may occlude the carotid or left subclavian artery.
Placed too caudally, the IAB may occlude the lumbar or mesenteric arteries and produce less-effective
counterpulsation. Daily radiographic assessment is prudent to detect catheter migration or a change of the aortic
contour suggestive of IAB-induced dissection.

**Gastric Access Tubes**

Whether inserted through the nose (NG) or mouth (OG), it is usually prudent to obtain a CXR to confirm gastric
tube position before administration of medication, fluid, or feeding, even when clinical evaluation indicates proper
positioning. Even in intubated patients, a small number of tubes intended for the stomach do end up in the lung
(usually the right mainstem bronchus). Vigorous insertion technique can force the gastric tube through the lung
into the pleural space. Inadvertent airway entry is most likely to occur when using a small-bore-stylet-stiffened
tube, especially when inserted in comatose or deeply sedated patients. When inserted via the esophagus, the
side holes of the enteral tube should be fully advanced past the lower esophageal sphincter to minimize reflux.
Following similar safety precautions, an abdominal film should be obtained after placement of a percutaneous
endoscopic gastric (PEG) tube to search for common complications, such as extragastric migration or peritoneal
leakage.

**Specific Applications of Chest Radiography**

As already mentioned the outset of this discussion, it must be recognized that the chest CT offers far greater
diagnostic precision than the bedside radiograph. Yet, for many purposes, the humble bedside chest radiograph
remains indispensible, being cheaper and quicker to obtain, presenting less exposure to ionizing radiation, and
sparing the patient the hazards associated with transport from the ICU environment.

**Atelectasis**

Atelectasis is a frequent cause of infiltration on ICU CXRs. The wide spectrum of findings ranges from invisible
microatelectasis, through plate, segmental, and lobar atelectasis, to collapse of an entire lung. Differentiating
between segmental atelectasis and segmental pneumonia is often difficult, because these conditions often
coeXist. However, marked volume loss, rapid onset, and quick reversal are more characteristic of acute collapse.
Atelectasis tends to develop in dependent regions and, more commonly, in the left rather than the right lower
lobe by a 2:1 margin. Radiographic findings of atelectasis include hemidiaphragm elevation, parenchymal
density, vascular crowding (especially in the retrocardiac area), deviation of hilar vessels, ipsilateral mediastinal
shift, and loss of the lateral border of the descending aorta or heart. Each lobe has a characteristic pattern of
atelectasis. With right upper lobe collapse, apical density increases as the minor fissure rotates superior medially
producing an easily recognizable curvilinear arch extending to the mediastinum. Because the left lung does not
have a middle lobe or minor fissure, upper lobe collapse occurs anteriorly, producing a diffuse haziness of the
hemithorax and loss of the upper left cardiac border. In both cases, the main pulmonary artery shadow moves
cephalad. On lateral CXR, right middle lobe atelectasis appears as a prominent wedge with its apex directed
toward the hilum, as the minor fissure and major fissure move toward each other. Unfortunately, on frontal films,
the findings are typically more subtle, often manifest only as obscuration of the right heart border. A lordotic film increases the density and sharpens the definition of the airless but thin right middle lobe. Partial collapse of either the right or left lower lobe produce similar patterns of diaphragmatic “silhouetting.” When lower lobe volume loss is extensive, a triangular posteromedial density can be seen with its base resting on the diaphragm. Contrary to popular belief, the “silhouette sign” is not always reliable on portable films, particularly in the presence of an enlarged heart or when the film was obtained in a lordotic or rotated projection. Air bronchograms extending into an atelectatic area suggest that collapse continues without total occlusion of the central airway and that attempts at airway clearance by bronchoscopy or aggressive suctioning, therefore, are likely to fail.

FIGURE 11-4. Appearance of a mobile pleural effusion in three positions. In the supine position, a “ground-glass” lateralized diffuse density (with preservation of vascular markings) may be the only sign of layered pleural fluid. A changing appearance with position confirms the diagnosis.

Pleural Effusion and Hemothorax

Pleural effusions occur very commonly among ICU patients; however, their appearances vary with body positioning (Fig. 11-4). On the supine AP CXR, large effusions redistribute—potentially causing a hazy density to overlie the entire hemithorax without loss of vascular definition (Fig. 11-5). Apical pleural capping is another radiographic sign of large collections of pleural fluid in the supine patient. Upright or lateral decubitus radiographs may help confirm the presence of an effusion (Fig. 11-6). If a large collection of pleural fluid obscures the lung parenchyma, a contralateral decubitus film often helps visualize the ipsilateral lung. Pleural fluid is not ordinarily visible until several hundred milliliters have accumulated. On lateral decubitus films, 1 cm of layering fluid indicates a volume that can usually be tapped safely. If there is any question about the quantity or mobility of fluid, bedside ultrasonography is usually helpful.
FIGURE 11-5. Mobile right pleural effusion supine. Diffuse haziness with well-preserved outlines of the ipsilateral pulmonary arteries are characteristic.

Subpulmonic or loculated fluid may be difficult to recognize. Hemidiaphragm elevation, lateral displacement of the diaphragmatic apex, abrupt transitions from lucency to solid tissue density, and increased distance from the upper left hemidiaphragmatic margin to the gastric bubble (on an upright film) are all signs of a subpulmonic effusion (Fig. 11-7). US and chest CT are useful adjuncts in detecting the presence of such collections of pleural fluid and in guiding drainage. US has the obvious advantages of portability, repeatability, cost efficiency, safety, and real-time imaging for drainage.

Extra-alveolar Gas/Barotrauma
Extra-alveolar gas can manifest as interstitial emphysema, cyst formation, pneumothorax, pneumomediastinum, pneumoperitoneum, or subcutaneous emphysema (see Chapter 8).

Pulmonary Interstitial Emphysema
Radiographic signs of gas in the pulmonary interstitium include lucent streaks that do not conform to air
bronchograms and new cysts at the lung periphery, usually at the bases. Interstitial emphysema may also generate small “target lesions” as air surrounds small peripheral pulmonary arterioles viewed en face. These signs, best seen when the parenchyma is densely infiltrated, portend the imminent (but not invariable) development of pneumothorax.

**Subpleural Air Cysts**

Subpleural air cysts, a potential sign of impending pneumothorax in mechanically ventilated patients, are small (3- to 5-cm wide) basilar rounded lucencies. The cysts often appear abruptly and tend to rapidly increase in size (sometimes to as large as 9 cm). Subpleural air cysts frequently progress to tension pneumothorax in the presence of continued high-pressure mechanical ventilation. The role of prophylactic tube thoracostomy remains undefined; however, when subpleural air cysts are noted, the clinician should reduce airway pressures to the extent possible and maintain a high level of vigilance and be prepared to emergently insert chest tubes. Fortunately, such catastrophic developments have become much less likely in the present era of lung-protective ventilation.

![FIGURE 11-6. Left: Bilateral pleural effusions with characteristic crescentic blunting on the upright PA film. Right: Mobile effusion in left lateral decubitus orientation. Arrows demarcate the fluid separating left lung from ribs.](Image)
FIGURE 11-7. A: Radiographic signs of a subpulmonic effusion (1) hemidiaphragm elevation with separation of lung from gastric bubble, (2) lateralization of the diaphragmatic dome, and (3) abrupt transition from lucency to soft tissue density. B: Left subpulmonic effusion in upright position. Note abrupt transition of density at the lung base and lateral displacement of what appears to be the hemidiaphragmatic dome.

**Pneumothorax**

Pneumothorax is often difficult to detect on portable CXRs. Relatively few ICU patients exhibit the typical patterns seen on upright CXRs performed in noncritically ill patients. Proper positioning assumes great importance in detection. On supine films or in patients with pleural adhesions, gas may collect exclusively in the basilar (anterior) regions of the thorax. Thus, gas may outline the minor fissure or may move anteriorly over the heart, mimicking pneumomediastinum or pneumopericardium. Loculated pneumothoraces can be very difficult to detect without CT, and it is surprising how many times residual localized air collections are found by CT among patients with one or more chest tubes. Radiographic signs of pneumothorax on the supine CXR include a “deep sulcus sign” and lucency over the upper portions of the spleen or liver (see Chapter 8). At the bedside, an upright *expiratory* CXR is often the best film for detecting a pneumothorax. This view confines a fixed amount of intrapleural air within a smaller volume, accentuating the proportion of thoracic volume it occupies and the separation of the lung from chest wall. Provider-implemented bedside US has facilitated such diagnoses and should be considered when doubt persists after CXR examination.

The visceral pleura provides a specific marker: a radiodense (white) thin stripe of appropriate curvature with lucency visible on both sides and absent lung markings beyond. Skin folds often mimic the pleural edge but can be distinguished by certain features: lucency present only on one margin, poorly defined limits, and extension beyond the confines of the rib cage. Because pneumothorax reduces blood flow to the collapsed lung, its density may be surprisingly normal, even with an extensive gas collection. Here again, failure to detect dynamic lung sliding and the presence of a lung point on US nicely complement or even supplant the radiographic evidence (see ICU Ultrasound, following).
Pneumothoraces are often characterized by the percentage of the hemithorax they occupy. This practice is highly imprecise, both because the frontal CXR is only two-dimensional and because apparent percentage changes occur with variations in breathing depth and position. As with pleural fluid, precise determination of the size of a pneumothorax is neither possible nor necessary. A tension pneumothorax (of any size) and a “large” pneumothorax both require drainage—the former because of its immediate physiologic effects, the latter because it creates a pleural pocket that is unlikely to reabsorb spontaneously over an acceptable time. The reabsorption rate of a pneumothorax has been estimated to be “1% to 2% per day,” a crude rule of thumb that emphasizes the slowness of this process. Thus, a 15% pneumothorax would typically take 2 weeks to reabsorb.

**TENSION PNEUMOTHORAX**

Action on a presumptive diagnosis of tension pneumothorax occasionally must be initiated solely on clinical grounds without imaging confirmation so as to address an advancing threat to hemodynamic stability. Radiographically, tension pneumothorax often shifts the mediastinum and flattens or inverts the hemidiaphragm ipsilateral to the pneumothorax. Yet, tension is usually difficult to diagnose with confidence on a single film; infiltrated or obstructed lungs fail to collapse completely, and an unyielding mediastinum may not shift noticeably, despite a marked pressure gradient. Comparison of past films and clinical correlation may be required. When doubt exists and the patient is hemodynamically unstable, emergent decompression is indicated.

The experience of past decades showed that pneumothorax occurs in up to 50% of patients receiving mechanical ventilation with peak inflation pressures exceeding 60 cm H\textsubscript{2}O, and a large fraction of those were under tension. The adoption of lower tidal volume ventilation has decreased the incidence of pneumothorax dramatically. When it does occur, pneumothorax commonly complicates the course of patients with necrotizing pneumonias, acute respiratory distress syndrome (ARDS), secretion retention, or expanding cavitary or bullous lesions. Tension pneumothorax may be very difficult to distinguish from bullous disease under tension by plain radiograph alone. Although a chest CT can be revealing, patients *in extremis* cannot wait for a diagnostic CT scan. In such emergent settings, erring on the side of chest tube insertion is probably the best course of action, even though rupturing a large bulla can create a bronchopleural fistula.

**Pneumomediastinum**

After gaining access to the mediastinum, gas normally decompresses into adjacent soft tissues. Apart from discomfort or pain, pneumomediastinum itself rarely produces important physiologic effects in adults. Mediastinal gas may arise from neck injuries, from rupture of the trachea or esophagus, or (most commonly) from alveolar rupture and retrograde dissection of air along bronchovascular bundles. Pneumomediastinum appears radiographically as a lucent band around the heart and great vessels as gas within the space separates the parietal pleura from the mediastinal contents. On the heart's inferior border, this lucency can extend across the mediastinum, linking the two sides of the chest with a "complete diaphragm sign." An unnaturally sharp heart border is the first indicator of pneumomediastinum, a sign that must be distinguished from the “kinetic halo” seen at the heart or diaphragm border of an edematous lung. The mediastinal pleura, outlined by gas on both sides of a thin radiodense line, can often be detected. On a lateral film, pneumomediastinum usually appears as a thin crescent of gas outlining the ascending aorta. Not uncommonly, extrapleural gas extends from the mediastinum, lifting the parietal pleura off the diaphragm, or outlining the inferior pulmonary ligament. Pneumomediastinum is an important harbinger of pneumothorax, which follows in up to 30% of mechanically ventilated patients. In doubtful cases where progression is feared, definitive diagnosis can be established by CT.

**Subcutaneous Gas**
In the adult, subcutaneous gas, also known as subcutaneous emphysema, usually has important diagnostic but little physiologic significance. Subcutaneous gas produces lucent streaks or bubbles in the soft tissues that contrast with the normal densities of the chest and neck. However, there is almost no limit to the path the gas may take, as it may track into the retroperitoneum, the peritoneal cavity, and even the scrotum. During mechanical ventilation, bilateral subcutaneous gas usually results from alveolar rupture and medial gas dissection, indicating both a viable decompression pathway and an increased risk of pneumothorax. Once pneumothorax has occurred, progressive accumulation of gas in the subcutaneous tissue suggests the presence of a bronchopleural fistula or a malfunctioning chest tube, especially if the gas is bilateral. Ipsilateral subcutaneous gas detected shortly after chest tube placement generally entered via the tube track itself. Subcutaneous gas detected immediately after blunt chest trauma should raise the possibility of tracheobronchial or esophageal disruption (see Chapter 36).

### Table 11-1. Radiographic Features of Pulmonary Edema

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cardiogenic or Volume Overload Edema</th>
<th>High-Permeability Edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart size</td>
<td>Enlarged</td>
<td>Normal</td>
</tr>
<tr>
<td>Vascular pedicle</td>
<td>Normal/enlarged</td>
<td>Normal/small</td>
</tr>
<tr>
<td>Flow distribution</td>
<td>Balanced/cephalad</td>
<td>Basal/balanced</td>
</tr>
<tr>
<td>Blood volume</td>
<td>Normal/increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Septal lines</td>
<td>Common</td>
<td>Absent</td>
</tr>
<tr>
<td>Peribronchial cuffing</td>
<td>Very common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Air bronchograms</td>
<td>Uncommon</td>
<td>Very common</td>
</tr>
<tr>
<td>Edema distribution</td>
<td>Even/central/gravitational</td>
<td>Patchy/peripheral/nongravitational</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Very common/moderate-large</td>
<td>Infrequent/small</td>
</tr>
</tbody>
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### Pulmonary Edema

Without invasive monitoring, distinguishing between normal permeability (fluid overload and congestive heart failure [CHF]) and high-permeability pulmonary edema, ARDS can be difficult. Considerable overlap exists in the radiographic findings of these entities, but certain CXR findings may be helpful in determining the etiology of excess lung water. These forms of edema are often distinguished by three features: size of the heart and great vessels, distribution of vascular markings, and the pattern of infiltration (Table 11-1). CHF and volume overload are characterized by a widened vascular pedicle, an even or inverted pattern of vascular markings, and a tendency toward a gravitational distribution of edema ("bat wing" or basilar). Pleural effusions, particularly those
of substantial size, are also more common with CHF than ARDS. The vascular pedicle is measured at the point the superior vena cava crosses the right main bronchus to a perpendicular dropped from the point of takeoff of the left subclavian artery from the aorta. Kerley B lines, because of perilymphatic interstitial fluid, are common in established CHF (usually of several days' to weeks' duration), whereas crisp air bronchograms are unusual. Conversely, the less mobile infiltrates of ARDS are widely scattered, patchy, and often interrupted by distinct air bronchograms. These criteria are better for correctly classifying CHF and volume overload edema and less accurate for identifying ARDS. Although useful when applied with appropriate clinical correlation, widespread application of these criteria to evaluate the etiology of pulmonary edema has shown them to be less reliable than stated in the original investigations. Because most of the radiographic deterioration seen in ARDS occurs within the first 5 days of illness, a worsening CXR appearance after this time suggests superimposition of pneumonia, fluid overload, CHF, or ventilator-induced lung injury (VILI).

Although pulmonary edema is usually bilateral and symmetric, it may collect asymmetrically when mediastinal tumor, bronchial cyst, or massive thromboembolism diverts flow preferentially to one lung. The recently transplanted lung is also prone to developing unilateral pulmonary edema. Asymmetry may also be observed following unilateral aspiration, reexpansion pulmonary edema, or in the presence of extensive bullous disease. Gravity may redistribute edema fluid and atelectasis to newly dependent lung regions over relatively brief periods after patient repositioning.

**Mediastinal Widening**

Mediastinal widening on a well-centered film (particularly following chest trauma or an invasive procedure) should raise suspicion of aortic disruption. (A rotated or lordotic film may be misleading.) A contrast-enhanced chest CT provides the definitive diagnosis. Obtaining a high-quality upright PA CXR, though desirable, is frequently not possible because of injuries or hypotension. Radiographic clues to aortic disruption include a widened superior mediastinum (the most sensitive sign), a blurred aortic knob, rightward deviation of a nasogastric tube or aortic shadow, and tracheal deviation to the right and anteriorly. Inferior displacement of the left main bronchus, left-sided pleural effusion (with or without apical capping), and displacement of intimal calcifications of the aorta provide other signs suggestive of aortic disruption (see Chapter 35). Mediastinal widening with vascular injury is frequently associated with traumatic fractures of the sternum, first two ribs, or clavicle. Widening of the cardiac shadow should prompt careful review of the aortic contour because blood may dissect from the aorta into the pericardium. If aortic disruption is suspected, angiography by catheter (the diagnostic “gold standard” for many years) is seldom needed. Contrast-enhanced CT scanning, MRI, and echocardiography almost invariably provide definitive evidence.

![FIGURE 11-8. Intraparenchymal versus intrapleural fluid collections. Fluid collections within the pleural](image-url)
space usually have a greater horizontal than vertical dimension, do not cross fissure lines, and may have sloping attachments to the pleural surface on one or more views. Furthermore, pleural collections typically have different dimensions on AP and lateral views. By contrast, intraparenchymal collections tend to be more spherical, with equal dimensions on AP and lateral views.

**Pericardial Effusion**

Pericardial effusion is recognized radiographically by enlargement of the cardiac shadow. The classic “water bottle configuration” of the cardiac silhouette, although highly characteristic, is unusual. An epicardial fat pad visible on the lateral CXR should raise suspicion of a pericardial effusion, as should splaying of the tracheal bifurcation. Echocardiography is the procedure of choice for the detection and evaluation of pericardial effusions, and it simultaneously affords the opportunity to assess heart chamber size, contractile function, and vena caval diameter. When a transthoracic echocardiogram cannot obtain images of adequate quality because of patient weight or chest hyperinflation, transesophageal echocardiogram is usually diagnostic.

**Air-Fluid Levels (Lung Abscess vs. Empyema)**

Several radiographic features help to distinguish whether an air-fluid level lies within the pleural space or within the lung parenchyma (Fig. 11-8). On an AP film, pleural fluid collections generate wide, moderately dense air-fluid levels, whereas intrapulmonary collections are usually smaller, more dense, and rounded. Lung abscesses and liquid-filled bullae tend to project similar diameters on both AP and lateral films (Fig. 11-9 Top panels). The air-fluid level of pleural fluid collections must abut the chest wall on either AP or lateral film (Fig. 11-9 Bottom panels). Fluid collections that cross a fissure line on upright films are located within the pleural space. Lung abscesses generally have distinct, thick, shaggy walls with irregular contours, unlike most liquid-filled bullae and pleural fluid collections. As body position is altered, pleural fluid collections frequently undergo marked changes in shape or contour. CT scanning reliably differentiates the two conditions.
Postthoracotomy Changes

After pneumonectomy, fluid accumulates in the vacant hemithorax over days to months. Whereas the absolute fluid level is of little significance, changes in the level of fluid are important. A rapid decline in the fluid level should prompt concern for a bronchopleural fistula, a complication that most commonly develops within 8 to 12 days of surgery. If a fistula develops earlier, failure of the bronchial closure should be suspected, prompting consideration of reoperation. Bronchopleural fistulas tend to displace the mediastinum to the contralateral side, an unusual occurrence during uneventful postoperative recovery. Small residual air spaces may remain for up to a year following pneumonectomy and do not necessarily imply the presence of a persistent fistula. Very rapid postoperative filling
of the hemithorax suggests infection, hemorrhage, or malignant effusion.

**Fistulous Tracts**

Fistulas between the trachea and innominate artery develop most frequently when a tracheal tube angulates anteriorly and to the right in a patient with a low tracheostomy stoma, persistent hyperextension of the neck, or asthenic habitus. Because of this association, anteriorly directed tracheal tubes should be repositioned. Fistulas also may form between the trachea and esophagus during prolonged ET intubation. These usually occur at the level of the ET cuff, directly behind the manubrium. Predisposing factors include cuff overdistention, simultaneous presence of a nasogastric tube, and posterior angulation of the tracheal tube tip. The sudden occurrence of massive gastric dilation in a mechanically ventilated patient provides an important clue. A radiographic contrast agent may be introduced into the esophagus after cuff deflation or tube removal in an attempt to confirm the presence of the fistula.

**Pulmonary Embolism**

Although the plain CXR rarely if ever diagnoses PE, it is quite useful to detect other conditions in the differential diagnosis including CHF, pneumothorax, and aspiration. Despite limited diagnostic utility, large emboli may give rise to suggestive findings: ipsilateral hypovascularity, pulmonary artery enlargement, and (rarely) abrupt vascular cutoff. Local oligemia (the Westermark sign) may be seen early in the course of PE, usually within the first 36 hours. “Hampton's hump,” a pleural-based triangular density caused by pulmonary infarction, is seldom seen. About 50% of patients with PE have an associated pleural effusion.

For critically ill ICU patients with suspected thromboembolism, it often makes sense to begin the evaluation with a Doppler examination of the limbs. If the US exam reveals what appears to be fresh clot in any deep vein, the diagnosis of “thromboembolism” is established, other tests are unnecessary as anticoagulation is indicated. It has become clear that for ICU patients not only are the legs a potential source of clot, but the neck and arms are as well. Roughly half of all CVCs in place for a week or more are associated with at least a partially occlusive thrombus, and approximately 15% of these patients have concurrent PEs. The initial use of limb US has several advantages, including avoidance of contrast exposure and travel from the ICU, as well as lower cost and limited interpretive turnaround time. If the US is negative but the clinical suspicion of PE remains high, ventilation/perfusion (V/Q) scanning or contrasted chest CT may be performed. The rarity of a normal CXR diminishes the value of V/Q scanning in the critically ill. Nonetheless, normal perfusion scans are very helpful, and abnormal scans help guide the angiographic search for emboli if the systemic contrast needed for CT is contraindicated by renal dysfunction. The sensitivity and specificity of chest CT for the diagnosis of PE are now well established. In the right clinical context, it is safe to assume that a large filling defect seen in the pulmonary circuit of a technically adequate study represents clot (i.e., high specificity). Primary tumors of the pulmonary artery, primary lung tumors, cancers metastatic to the mediastinum, nonneoplastic mediastinal adenopathy, hydatid disease, and mediastinal fibrosis rarely can mimic PE. By contrast, because the sensitivity of CT varies among institutions, and even in the best centers is not 100% for subsegmental clots, a negative CT should not be regarded as definitive data excluding PE. Sensitivity is optimized by a scanner with many rows of detectors, quick acquisition time, optimal contrast injection technique and gating, adequate breath-holding by the patient, and experienced interpretation of optimally reconstructed images including three-dimensional views. Although there is controversy about the importance of subsegmental clots in healthy patients, in critically ill patients with impaired cardiopulmonary reserve, it is probably inadvisable to overlook such emboli. Echocardiogram may reveal right ventricular and pulmonary arterial dilation. If the Doppler US is negative, V/Q not practical, echocardiography unrevealing, and CT nondiagnostic while clinical suspicion remains high, angiography is the next, seldom taken step. Frequently, CT and catheter angiography...
are both contraindicated by renal insufficiency. Angiography can be safely performed in most critically ill patients, provided that: (1) care is used in transport, (2) pulmonary artery pressures are not excessive at the time of contrast administration, and (3) selective injections guided by perfusion scanning are performed. Septic PE should be considered in patients with multifocal cavitary lesions of varying size. A complete discussion of thromboembolism diagnosis is presented in Chapter 23.

**Pneumonitis**

**Aspiration and Acute Pulmonary Edema**
Although bacterial infection sometimes supervenes, gastric aspiration initially produces a sterile chemical pneumonitis. When bacterial infection complicates aspiration in the intubated patient, the time from intubation to aspiration can provide valuable clues to the etiologic organism. Events occurring within 4 days of intubation are usually associated with *Staphylococcus*, *Streptococcus*, and *Haemophilus* infections, whereas later episodes are usually because of gram-negative rods. Massive aspiration, although position and volume dependent, typically appears as bilateral diffuse alveolar and interstitial infiltrates of rapid onset. The extent of the infiltrate does not correlate with outcome, and radiographic improvement often occurs quite rapidly. Aspiration in the supine position usually affects the perihilar regions and superior and basilar segments of the lower lobes. Patients who aspirate in a decubitus position often develop unilateral infiltrates. When asymmetrical, the right lung is usually more involved. Significant atelectasis may occur when large pieces of solid food or foreign objects (e.g., teeth, dental appliances) are aspirated.

On occasion, massive symmetrical aspiration and/or ARDS can be difficult to distinguish from acute pulmonary edema (Fig. 11-10). As discussed in Chapter 24, several CXR cues may help in making that distinction. Blurred hilar structures and the virtual absence of air bronchograms characterize acute pulmonary edema and fluid volume overload.

**Pneumonia**
Although the CXR is never diagnostic microbiologically, it may give a clue to the organism producing bacterial pneumonia. Common bacterial pathogens typically produce patchy segmental or lobar involvement. Bulging fissures, although uncommon, suggest *Klebsiella*. A diffuse, patchy, “ground-glass” appearance suggests *Legionella*, *Mycoplasma*, or *Pneumocystis*. Small, widely scattered nodular densities suggest *Mycobacterium tuberculosis* as the etiological organism. Larger nodular densities are associated with *Cryptococcus*, *Actinomycosis*, or *Nocardia*. *Aspergillus* often gives rise to peripheral wedge-shaped infiltrates caused by vascular invasion and secondary infarction or cavitary formation. Cavitation suggests neoplasm, tuberculosis, fungal infection (e.g., histoplasmosis, cryptococcosis, coccidioidomycosis), lung abscess, or septic PE. Pneumonitis that develops in preexisting areas of bullous emphysema often produces air-fluid levels that can be confused with lung abscess or empyema. The thinner contour of the cavity wall, the more rapid pace of development and resolution, and premorbid CXRs demonstrating bullae help to identify this problem.
Nosocomial- or ventilator-associated pneumonia affects up to 30% of patients with ARDS but is difficult to detect with certainty because focal parenchymal densities may represent edema, atelectasis, and infarction, as well as infection. Hence, radiographic abnormalities must be interpreted in light of the clinical situation. A new unilateral infiltrate in a patient with a previously stable CXR is the best radiographic indicator of a superimposed infection; however, fever, increased sputum production, and progressive hypoxemia are better indicators than the CXR alone. A focal wedge-shaped infiltrate (especially occurring distal to a PAC tip or in a patient with hemoptysis) is likely to represent pulmonary infarction.

**Intra-abdominal Conditions**

The upright CXR can also help diagnose acute intra-abdominal problems. Midline or paraesophageal hiatal hernias usually pose little diagnostic problem. Diaphragmatic disruption may allow abdominal contents to
herniate into the chest following abdominal trauma, often displacing a gas-containing viscus into the left chest. When safe to administer, oral contrast aids in the diagnosis during the CT scan. Short of a trip to the CT scanner, the upright CXR also provides the most sensitive method of detecting free air within the abdominal cavity. (A cross-table film of the abdomen taken at least 5 minutes after decubitus positioning may serve a similar purpose.) Intubated patients frequently swallow air, producing gastric dilation. In the appropriate setting, massive gastric dilation can suggest the possibility of esophageal intubation or a tracheoesophageal fistula.

CT AND MRI

Expanding Imaging Potential—Reconstruction, Multiplanar, and Subtraction Views

Scanning and digital analysis have undergone an important transformation over the most recent decade. Using data from a single acquisition of CT data, images obtained without or preferably with contrast can be reconstructed to view multiple planes—not only the traditional axial plane but also the coronal and sagittal ones, allowing improved diagnostic accuracy (Fig. 11-11). Moreover, subtraction techniques may highlight the vasculature (Fig. 11-12). Three-dimensional reconstructions may be developed from the CT database that proves of high value in detailing the anatomy of difficult cases. Such helpful innovations were unavailable before the accelerated development of digital radiography.

General Preparing of the Patient for Imaging Studies

Radiology staff performing these exams will facilitate and help implement their preparation, depending on the study being performed. Restricted angulation of the imaging table or gantry is often a limiting factor for patients who are not intubated and receiving mechanical support. If the patient is to undergo a sedation-based procedure such as drain placement, then a prior coagulation profile and NPO status are prerequisites. With elective procedures, the clinician must plan ahead or defer transport in order to comply with these requirements and imaging suite schedules. It is wise to check verbally with the technical staff whenever there is doubt regarding the demands and timing of the study or procedure.

Computed Tomography

Establish urgency of exam (stat vs. routine). The exam is usually protocolled by the radiologist, and the selected protocol then helps determine the appropriate prep. Depending on the exam, the patient may need oral contrast (e.g., CT abdomen), which can be administered via enteric tube, if necessary. Establish appropriate IV access for IV contrast administration provided that it both indicated and not prohibited by allergy or renal insufficiency. If CTA is ordered, then the type (and patency) of IV access catheter may need to be approved by CT staff, as this study requires a relatively high injection rate of the contrast with elevated risk of IV contrast extravasation/infiltration. Communication with the radiology staff prior to transport is usually advisable.

Magnetic Resonance Imaging

Because it invariably takes a relatively long time to complete, MRI is generally avoided in ICU patients unless both clinician and radiology team believe it to be absolutely necessary. Unstable and tenuous patients are placed at particular risk because of the relative separation of patient from caregivers. Confer with the MR tech and/or radiologist to discuss how best to proceed. Individual patients may pose unique limitations.

Ultrasound

Ultrasound imposes very few limitations other than physical restricted access to appropriate acoustic windows from binders, wounds, and dressings. For many purposes, high-quality ultrasonic examinations are acquired by technicians at the bedside. Abdominal and pelvic imaging are preferably done in an NPO state to limit bowel gas from interfering with the imaging.
FIGURE 11-11. Top: The two-dimensional imaging planes. The “transverse” plane is also termed “axial.”
Bottom: Three planes of view for head CT.

Chest CT and MRI

The chest CT finds many applications in intensive care unit practice, particularly when contrast can be used to highlight the vasculature and sharply distinguish parenchyma from pleural space. Often, CT is the only practical way to image the lung in very obese individuals, as the bedside CXR cannot adequately penetrate the chest wall to reveal the obscured lung characteristics. It is prudent, therefore, for all critical care unit practitioners to become familiar with the basic elements of axial chest CT interpretation (Fig. 11-13) and to be aware of coronal and sagittal plane reconstructions (Fig. 11-14A and B).

Although indispensable to modern critical care practice, CT scanning (and MRI) has significant limitations in the critically ill population. Continuing technical advancements in modern CT scanners expedite the process of image acquisition...
and in-suite interpretation. Appropriate concern has been voiced over the risks of moving patients out of the ICU for imaging studies; however, carefully arranged transport is routinely performed reasonably safely. The range of physiologic changes observed in patients transported to radiology suite is comparable to that of patients who remain in the ICU for a similar time. The most important feature of safe transport is to ensure that all vital supports can be effectively maintained and that adequate equipment and personnel are immediately available to cope with any catastrophic event (e.g., accidental extubation or extraction of venous or arterial catheters or chest tubes, interruption of critical infusions, unanticipated cardiac arrest). Patients with bronchopleural fistula needing continual pleural drainage and those requiring vasopressors or high inspired oxygen concentrations or PEEP are at particular risk. It is important to be sure that the intubated patient is able to be adequately oxygenated and ventilated on the transport set-up for several minutes before departure. Although now rarely used in transportable patients, interruption of inhaled nitric oxide or nebulized prostacyclin infusions during transport can precipitate calamitous physiological deterioration. Metallic appliances create artifact on CT scans and may preclude use of MRI because of the powerful magnetic fields involved. Furthermore, MRI studies are especially time consuming, and the inability of critically ill patients to remain adequately immobile may produce unacceptable motion artifact unless neuromuscular blocking agents are used.
FIGURE 11-12. **A:** Multiplanar 3D reconstruction of circle of Willis using data from a single CT study and subtraction technique. Such images can be rotated around a selected axis. **B:** Multiplanar reconstruction of the heart with ECG gated subtraction views of main coronary vessels. **C:** Multiplanar reconstruction of abdominal vasculature with subtraction, highlighting of selected organ vasculature.
FIGURE 11-13. Top: The normal structures visualized by a vascular-contrasted axial CT image at the carinal level. Bottom: The normal cardiac structures visualized by a vascular-contrasted axial CT image at the midchest level.
CT scanning often requires use of nephrotoxic contrast material. (Enteral contrast used for abdominal scanning does not carry this risk.) Prophylaxis of the patient with marginal renal function is highly variable but should include at least adequate hydration; from this standpoint, sodium bicarbonate may be preferable to the chloride load of saline. Acetylcysteine may be effective, but evidence is conflicting. In years past, MRI was used in place of CT for patients with marginal renal function in an attempt to avoid contrast nephrotoxicity. Unfortunately, the use of some gadolinium-based MRI contrast media may be even more dangerous. Gadolinium has been associated with a progressive often devastating scleroderma-like syndrome known as progressive nephrogenic sclerosis. Many features of this syndrome remain uncertain; therefore, until this condition is better understood, it is probably prudent to use gadolinium contrast sparingly and attempt to avoid it in patients with renal insufficiency.

The financial aspects of imaging should not be overlooked. A chest CT scan typically costs three to four times as
much as a portable CXR in addition to the costs of transport, which can be substantial. Because patients are placed at higher risk during travel and there are significant financial and manpower costs involved, it is logical to plan ahead by bundling studies together when feasible. For example, if an elective head CT is planned tomorrow but an urgent chest CT must be done today, it may make sense to perform both studies today, avoiding the second trip. As a corollary, if an imaging study is likely to yield results that will prompt a radiology-based intervention (e.g., needle or catheter aspiration), it is common sense to confer with the radiologist in advance of the transport, so as to arrange rapid interpretation of the diagnostic study and subsequent intervention in a single trip. Simple preplanning can also avoid wasteful, redundant studies. For example, if a chest CT is to be performed today, there is little reason to do a “routine” morning CXR.

In neurocritical care applications, the noncontrasted CT excels for diagnosis of acute intracranial bleeding. It is also helpful when determining if there is an intracranial mass prior to a lumbar puncture and for detecting sinus cavity opacification. However, detailed anatomical imaging of the brain, spinal cord, and other soft tissues is best performed by MRI (Fig. 11-15). Moreover, detection of acute ischemic strokes by CT is not reliable until many hours have passed after the event (Fig. 11-16A), and inflammation of the meninges may evade notice. For these selected problems, the MRI is better adapted, as it is immediately sensitive to both (Fig. 11-16B). With different radio frequency stimulation and pulsing sequences (so-called “weighting,” Fig. 11-17), MRI can reveal inflammation and edema (T2 and flair weighting) and perfusion adequacy (diffusion weighting).
FIGURE 11-15. Sagittal MRI imaging of brain and spinal cord. Note the fine anatomic detail provided by T1 weighting.
FIGURE 11-16. A: Time dependence of imaging ischemic stroke by unenhanced CT in patient presenting with new-onset neurologic deficit. The large ischemic zone was not evident on the earlier study. Arrows delineate compromised zone (Left: upon admission; right: after 36 hours). B: Comparison of near-simultaneously obtained head CT (left) and diffusion-weighted MRI (right) of a patient with ischemic (right hemispheric) stroke.

Despite limitations, the chest CT often provides information not otherwise available. It frequently reveals a small or loculated pneumothorax in patients when previous CXRs are unrevealing. Chest CT also aids discovery of lung abscess or empyema and usually can differentiate between the two conditions. In patients with empyema and persistent, unexplained fever or with a persistent pneumothorax, the chest CT is invaluable to evaluate the location and effectiveness of thoracic drainage tubes. From a scientific standpoint, CT scanning has added greatly to our understanding of the distribution and positional kinetics of acute lung injury (ARDS). CT scanning also demonstrates the severity and distribution of regional barotrauma, offering insight into the potential deleterious effects of excessive airway pressure. Normal-appearing lung is seen immediately juxtaposed with densely infiltrated lung. These normal-
appearing and presumably normally compliant lung units are likely to be overdistended or overstrained by elevated positive pressure, whereas densely infiltrated lung is likely to remain atelectatic. The physiologic result is shunting of blood past atelectatic alveoli and overdistention of other alveoli, predisposing them to rupture or VILI.

FIGURE 11-17. Options for MRI display (normal brain, axial view). T1-weighted brightness corresponds to fat content, and details the anatomy particularly well. T2 weighting tends to highlight pathology associated with higher water content, such as cerebral edema or inflammation. The Flair image attenuates the CSF brightness of the T2 image and therefore is particularly helpful in distinguishing details of pathology. Diffusion-weighted images (DWI, not shown) are the best option for distinguishing well perfused from ischemic tissues, as in early stroke.

In summary, the chest CT represents one of the most useful diagnostic tests available to intensive care practitioners. A short list of indications for chest CT scanning include (1) evaluation of thoracic trauma, (2) searching for occult or persistent sources of fever (empyema, lung, or mediastinal abscess), (3) guiding placement of drainage tubes for loculated or persistent pneumothorax or pleural effusions, (4) detecting mediastinal pathology (especially in the presence of parenchymal infiltrate), and (5) searching for pulmonary emboli.

ABDOMINAL RADIOGRAPHY

Abdominal CT and Screening Films (KUB)

Because plain abdominal X-rays have largely been replaced by the abdominal CT scan, it is prudent for the acute care practitioner to become familiar with its essential elements (Fig. 11-18). The use of abdominal US and CT scanning is discussed in detail, as it relates to specific disease entities in Chapter 36. The standard examination of the abdomen, consisting of supine kidney-ureter-bladder (KUB) or “flat plate” and upright views, can still be useful and does not require a trip outside the ICU. If an upright film cannot be taken, a lateral decubitus view may be substituted. Systematic review of the KUB may furnish important information, especially after trauma. Fractures of the lower ribs on the left suggest the possibility of a ruptured spleen or lacerated kidney as does medial displacement of the gastric bubble. Breaks in lower ribs on the right suggest the possibility of renal or hepatic damage. Fractures of the lumbar spine, pelvis, and hips may be seen as “incidental” findings on plain abdominal radiographs in trauma patients. A ground-glass appearance, displacement of the retroperitoneal fat stripe, or centralization of gas shadows suggests ascites or hemoperitoneum. Free air usually indicates a ruptured viscus, gas-producing infection, barotrauma-induced
or postoperative change. Free air is much more commonly seen as the result of upper GI (stomach or duodenum) perforation rather than from colonic perforation (diverticulitis, appendicitis, colon cancer).

FIGURE 11-18. Normal anatomic structures visualized on an axial abdominal CT.

The KUB view is a poor indicator of liver size, and when in question, should not supplant careful physical examination or CT evaluation. The gallbladder is inadequately defined on the KUB view unless it is very distended or calcified. Less than 15% of gallbladder calculi are visible. Gas appearing in the biliary ducts is highly suggestive of infectious cholangitis but can occur following endoscopic retrograde cholangiopancreatography. The ingestion of massive amounts of carbonated beverages, or intake of compounds that can generate gas when mixed with gastric acid (e.g., sodium bicarbonate), can also cause bile duct gas. Hepatic calcifications, although rare, may occur due to healed infection, hemangioma, or metastatic carcinoma. Films taken in different positions may help sort out the location of right upper quadrant calcifications. Calcifications within the kidney or liver maintain a relatively fixed position, whereas stones within the gallbladder are usually mobile. Use of the KUB view in the diagnosis of the “acute abdomen” is discussed in Chapter 36.
Findings Relevant to Specific Organs

Kidneys and Ureters
The visibility of the kidney on the KUB view depends on the amount of perinephric fat and overlying bowel gas. The combination of kidney enlargement and calcification suggests urinary tract obstruction or polycystic kidney disease. If nephrolithiasis is suspected, the renal outlines and course of both ureters should be carefully inspected for calculi (visible in up to 85% of cases). Identifying gas in the renal pelvis is uncommon but is indicative of emphysematous pyelonephritis seen most often in poorly controlled diabetics. Gas-producing infections of the bladder are also seen occasionally.

Pancreas and Retroperitoneum
Asymmetric obliteration of the psoas shadows or retroperitoneal fat lines suggests a retroperitoneal process (most commonly pancreatitis or hemorrhage from a leaking aorta). Similar changes can be seen with spontaneous hemorrhage or traumatic disruption. Although the pancreas is not normally seen on the plain radiograph, calcifications may occur in chronic alcoholic pancreatitis. Localized areas of ileus over the pancreas, such as the “colon cut-off sign” and the “sentinel loop,” may also help in the diagnosis of pancreatic inflammation.

Stomach and Bowel
The stomach normally contains some fluid and air, but massive gastric dilation suggests gastric outlet obstruction, gastroparesis, or esophageal intubation. By contrast, the small bowel normally contains little air; gaseous distention indicates ileus or small bowel obstruction. Air-fluid levels of different heights within the same loop of small bowel on an upright film usually indicate mechanical small bowel obstruction and imply residual peristaltic activity. Fluid levels at the same height in a loop of bowel do not necessarily indicate mechanical obstruction. Absence of colonic or rectal gas in patients with small bowel air-fluid levels strongly suggests complete obstruction of the small bowel with distal clearing of gas. Conversely, the presence of gas in the colon (except for small amounts of rectal gas) all but excludes the diagnosis of complete small bowel obstruction. (Incomplete obstruction may be present, however.)

Colonic obstruction because of a sigmoid volvulus may be diagnosed via a KUB view that shows massive sigmoid dilation; the sigmoid forms an inverted “U” whose limbs rise out of the pelvis. Apposition of the medial walls of these bowel segments produces a midline soft tissue density whose inferior extent approximates the site of torsion. A variety of conditions leading to ICU admission may produce colonic pseudo-obstruction (Ogilvie syndrome) in which massive colonic dilation occurs due to diminished parasympathetic activity (see Chapter 36). Radiographically, the CT demonstrates the absence of a distinct transition point, and unlike the frequently encountered adynamic ileus, affects the small bowel to a lesser degree. Although usually managed conservatively, cecal dilatation to greater than 12 cm suggests the possibility of impending perforation and prompts decompressive interventions.

The frequently observed sign of “thumb printing” is a useful, highly significant but nonspecific sign of large bowel wall thickening that is most closely associated with ischemia. These nodular indentations appear at regular intervals along the bowel wall and may originate from bowel inflammation (Crohn disease or ischemic colitis, C. difficile or pseudomembranous colitis, diverticulitis) or more chronically in such noninflammatory conditions as lymphoma and amyloid. When seen in conjunction with massive colonic dilation and supportive abnormalities of vital signs, toxic megacolon is highly likely.

Peritoneal Cavity
On the supine abdominal radiograph, ascites is demonstrated by diffuse haze, indistinctness of the iliopsoas stripes, centralization of small bowel segments, and abnormal separation of bowel loops. Increased pelvic density characterizes ascites on the upright film.

Abnormal gas collections are recognized by their nonanatomic location. Therefore, all gas densities on supine and erect films require explanation. Each must be assigned to an anatomic segment of bowel. Gas may collect under the diaphragm or overlie the liver on erect or lateral decubitus films, respectively. Free air also allows visualization of both sides of the walls of gas-filled bowel. “Bubbly,” curvilinear, or triangular gas collections between segments of bowel suggest abdominal abscess. Bowel ischemia may produce a characteristic pattern known as pneumatosis cystoides that represents gas within the bowel wall. Rarely, pneumatosis may rupture to produce free intraperitoneal air, simulating a perforated viscus. Bowel ischemia is more confidently diagnosed when thumb printing is observed.

**ACUTE CARE ULTRASOUND**

Few areas of critical care practice have been adopted as quickly or impacted care as profoundly as the bedside application of US imaging by the clinician. Although its full potential for diagnosis and monitoring continue to be actively explored, dramatic advantages have become apparent for settings as diverse as cardiopulmonary arrest to weaning from mechanical ventilation. Its major benefits include portability, lack of radiation hazard, speed of data acquisition, low cost, serial repeatability, and ability to interrogate dynamic properties of the lungs and heart by two-dimensional and time-based (M-mode) imaging displays. Development and deployment have been especially rapid in the general diagnostic categories of acute dyspnea, trauma, and shock. US has proven itself to be an invaluable aid in vascular cannula insertion (venous and arterial) as well other bedside procedures, both facilitating those otherwise time-consuming interventions and preventing hazardous misadventures. Because answers usually come quickly, US saves valuable time and guides the path through the diagnostic decision tree, avoiding unnecessary delays and costly tests. For patients who are difficult or risky to transport, the portability and capability of US may obviate moving them outside the emergency suite or ICU environments. As US has become more generally deployed, the library of sonographic findings associated with key pathologic findings has been expanded and detailed. Stepwise bedside US examination sequences, or “protocols,” have been developed that use these signatures to logically and comprehensively assess a number of urgent ICU problems. US for the acutely ill patient is usually categorized into these broad headings: thoracic, abdominal, cardiac, and vascular.

**Limitations of Clinician-Applied US at the Bedside**

Despite its high value and negligible hazard, acute care ultrasound (ACUS) is not the ultimate diagnostic tool. The inherent limitations of US itself have been apparent ever since consultant-provided echocardiography was first introduced to clinical practice. An adequate ultrasonic window may be obscured or degraded by massive obesity, bone, dressings, or hyperinflated lung. The penetration depth of US is restricted, and although the probe is easily repositioned, access points and acoustic windows are limited. Furthermore, only confined sectors and tissue “chunks” are imaged at a given site. Detailed and three-dimensional imaging in the critically ill remains the province of CT, fluoroscopy and, to a lesser extent, MRI. Thus, although US often serves to rule in and rule out certain broad possibilities, there are a more restricted number of situations for which it provides the incontrovertibly precise diagnosis. Bedside US, then, often serves as an initial probe for (or complement to) more established and often more precise diagnostic tools, rather than a replacement for them. Nonetheless, US speeds and facilitates the diagnostic process. For many purposes (e.g., chest tube insertion), US precludes the need for radiation or contrast, promotes early intervention, and encourages repeated cost-effective monitoring of progress. Operator proficiency at performing and interpreting bedside US ultimately determines the value or
interpretive error of this methodology. Although these skills cannot be acquired without successful “hands on” training and practical clinical experience, the potential and technical backgrounds for US are important to understand.

FIGURE 11-19. Long and short axes of the heart used in cardiac ultrasound (echocardiography).

Problem Categories and Protocols

Cardiovascular ACUS

Detailed ultrasonic examination of the stable patient with heart disease continues to be best assigned to consulting cardiologists who formally evaluate detailed echocardiograms acquired with high capability equipment (Fig. 11-19). In emergency settings and for targeted critical care purposes, however, provider-implemented ACUS can be of high value to direct further steps in management. A fundamental knowledge of acoustic windows and structural imaging correlations is quickly becoming an essential skill for the intensivist (Fig. 11-20A and B). Large pericardial effusions and gross deficiencies or asymmetries of ventricular filling, for example, are readily detectable through one or more acoustic windows, as are the noncompressible femoral veins of a fresh lower extremity clot. Pericardial effusions or blood clots within the pericardium do not move with the heart, whereas the epicardial fat pads do. Descriptive technical details of how to perform such studies are readily available from comprehensive published review articles and educational online videos and will not be attempted here.
Increasingly, US imaging has become integrated into everyday practice. ACUS provides considerable data relevant to the diagnostic evaluations of shock and its resuscitation. Clearly, the possibilities of obstructive shock (pericardial tamponade, massive PE, and pneumothorax) and certain forms of cardiogenic shock can be interrogated by measures already described. Cardiac filling status is effectively assessed by determining inferior vena cava dimensions (ideally >2 cm), respiratory variations in its diameter, and tendency to collapse with probe compression. Moreover, in decisions made to administer or withhold additional fluids in shock states, the wisdom of doing so may be brought into question by the appearance and subsequent multiplication of B lines that indicate the development of interstitial and alveolar edema. These may appear before vital signs change or clinical signs develop. A number of protocols have been proposed to guide fluid administration in a variety of shock states by practitioner-driven ACUS (e.g., FALLS). Although all are rational and appear in practice to offer benefit, evidence-based validation for any has been limited.

FIGURE 11-20. A: Apical 4-chamber view obtained with 2D cardiac ultrasound. B: Longitudinal axis view of left heart and aorta by cardiac echo.
Ultrasound may be of considerable value during cardiopulmonary resuscitation (CPR) as it can be applied during noncompressive periods (pulse checks) to quickly identify potentially reversible causes or perpetuators of cardiac arrest such as extreme hypovolemia, acute cor pulmonale, pericardial tamponade, and tension pneumothorax. Failure of the heart to contract despite electrical activity and lengthy period of CPR support portends a dismal outcome and strongly supports a decision to abandon the attempt to restore effective spontaneous circulation.

**FIGURE 11-21. Left:** A lines (red arrows) are the diminishing ultrasonic reverberations of the pleural stripe (white arrow) through normal lung tissue. **Right:** B lines are linear streaks (yellow arrow) emanating from the pleural boundary. These indicate increased tissue water, such as caused by edema.

**Thoracic Ultrasound**

Until quite recently, the apparent artifacts on 2D images caused by sonic interactions of tissue and air were disregarded, despite their high diagnostic value. Assuming the use of appropriate probe, depth, and ultrasonic frequency range, normal lung, pneumothorax, and edematous, consolidated, and liquid-filled spaces return characteristic sonograms that vary during tidal breathing (Fig. 11-21). Sliding of the visceral pleura at its interface with the fixed parietal counterpart as well as repetitive curvilinear lines that fan out parallel to the pleural surface (A lines) is characteristic of normal lung. A limited number of hyperechoic, self-erasing lines orthogonal to the pleural plane (B lines or lung rockets) are produced by interstitial lung edema. When B lines are profuse, evenly distributed, and bilateral, alveolar edema likely is present. The homogeneous, sharply demarcated, homogeneous and distinctly opaque sonographic shadow separating the parietal from the visceral pleura indicates an uncomplicated pleural effusion. A sinusoidal profile is usually generated during M-mode US (Fig. 11-22). Measuring a pleural liquid depth of greater than 1.5 cm indicates that needle thoracentesis can be safely performed at that site. US is essential to safely perform needle insertion when the patient is receiving mechanical ventilation or when the effusion is loculated.

A pneumothorax is characterized by an echo-free separation between the lung and chest wall. Confirmation is made when a motionless probe detects phasic (tidal) transitions during tidal breathing between echo free and lung signatures. This “lung point” is confirmed by a “seashore”-like appearance on continuous M-mode tracing (Fig. 11-23).
Use of these characteristics in conjunction with limited cardiovascular ultrasonography directed toward leg clotting and right ventricular dilation is made in systematic protocols designed to rapidly determine the cause of acute dyspnea (e.g., the BLUE protocol). Thoracic interrogation is performed sequentially at three sites (anterior, lateral, and posterolateral) in the semirecumbent patient as evidence is sought for pneumothorax, lung edema, and consolidation or lung collapse. US of the cardiac and femoral zones completes the appraisal.
patterns during the phases of the breathing cycle (C).

Vascular Catheter Placement

Bedside US has become an indispensable aid in placing central catheters and arterial lines, both speeding the process and reducing hazard and discomfort. During the procedure and once placed, the catheter usually can usually be distinguished from the targeted vessel, confirming successful vascular entry or alerting the clinician to malpositioning. Immediate postprocedural thoracic US following jugular and subclavian punctures may alleviate concerns of procedure-related pneumothorax if the signs of “lung sliding” and clear A or B lines signs are detected. US has become an integral adjunct to PICC placement from the brachial sites in difficult cases (e.g., upper extremity edema). Provider-performed US of the upper extremity may be serially conducted when concern arises regarding the possible development of upper extremity thrombosis. Confirmation of clot presence or absence, however, should usually be sought by formal US consultative studies.

Abdominopelvic Ultrasound and FAST Scanning

Apart from diagnosis and treatment of ascites, US of the abdomen and pelvis has proven its value in the emergency department and ICU for evaluations of sepsis of indeterminate source, acute undifferentiated abdominal pain, and suspected viscus or abdominal aneurysm rupture. Questions regarding gallstone, cholecystitis, urinary tract obstruction, soft tissue infections, and free fluid or air collections may first be noninvasively approached using this methodology. Although gas detected in the biliary tree may appear after ERCP or after remote biliary surgery, its detection in the setting of abdominal sepsis often suggests life-threatening infection. Emergency abdominal US in adults with abdominal trauma (focused assessment with sonography for trauma [FAST]) is a widely used management-directing US survey whose results are more reliable after presentations for blunt rather than penetrating trauma (Fig. 11-24). The main goal is to detect newly developed pericardial, intrathoracic, or intraperitoneal free fluid. Acknowledged limitations are that FAST is less sensitive for pelvic bleeding, does not interrogate the retroperitoneum, and cannot reliably differentiate the nature of what caused the pathologic fluid collection (blood, urine ascites). Points of sonographic access (windows) are used to evaluate the pericardial, peritoneal, and pleural cavities. Unless a pointed indication interrupts the order, the examination sequence reflects the severity of potential life-threatening risks. The heart is assessed for the presence of cardiac tamponade, global wall motion abnormalities and other evidence of injury, and the adequacy of right ventricular filling.
After the heart and pericardium, the right flank (hepatorenal view or “Morison pouch”), left flank (perisplenic view), pelvis, and thorax (pneumothorax and hemothorax) are evaluated. The liver, spleen, and partially filled bladder provide the necessary sonographic windows. The abdominal sequence leads with the right flank and gutter before the left flank and gutter exams because blood originating from both splenic and hepatic trauma must first pass through the Morison pouch on before collecting in the more dependent pelvic cavity.

As in other applications ACUS, the FAST protocol should be considered to provide very useful but often not sufficiently definitive information to preclude radiologic studies or even exploratory surgery. Some serious injuries are seldom visualized confidently by US (e.g., aortic and diaphragm tears, pancreatic lesions, bowel perforations, mesenteric trauma, and injuries that do not produce free fluid in amounts >250 mL). Fluid acutely collected in the pelvis may be either urine or blood. Although important penetrating injuries may go unsuspected with the initial evaluation, overall sensitivity of FAST in these and for all abdominal injuries may improve by performing serial
INTERVENTIONAL RADIOLOGY FOR CRITICAL CARE

Interventional radiology is another imaging discipline whose indications have dramatically increased for the past decade. Dynamic imaging capabilities such as C-arm fluoroscopy and angiography combined with elegant 3-dimensional reconstructions, precise localization, and an ever-expanding arsenal of catheter-based devices and stents now enable performance of high-value, low-morbidity procedures. These include otherwise routine cannulation procedures that cannot be attempted successfully at the bedside as well as many sophisticated therapeutic procedures that stabilize hemorrhage, relieve ischemia, and obviate the need for high-risk operative intervention. Broadly speaking, the major purposes are usefully classified as vascular and nonvascular in nature. The vascular indications include troublesome bleeding in need of control by embolization of the appropriate arterial source and the extraction of thrombi and placement or manipulation of intravascular catheters. Endovascular stent placements may be lifesaving (e.g., aortic dissection and transjugular intrahepatic portosystemic shunt [TIPS] procedures for portal decompression [Fig. 11-25]). Nonvascular indications for IR generally involve drainage of an infected pocket, placement of stents, feeding tubes, and super pubic catheters. The IR service should be engaged early in the decision-making process, particularly when surgical intervention is a contemplated alternative option. Although the range of problems and potential solutions is already vast and continually expanding, certain of these deserve mention here.

Vascular Interventions

Hemorrhage and Ischemia

A wide variety of life-threatening hemorrhagic events can be effectively addressed by angiography followed by embolization of the culprit vessel (Fig. 11-26). These sources commonly involve the bronchial, GI/mesenteric, or solid organ distributions. Control is routinely achieved, whereas infarction of the embolized tissue occurs only very rarely.
Insertion and deployment of endovascular stent repair of aortic aneurysm.

Type B aortic dissections accompanied by indications for emergent/urgent correction can frequently be addressed by IR-directed stent placement.  (Fig. 11-27). End-organ ischemia of cerebral, extremity, mesenteric, or renal systems may often be effectively relieved by thrombus extraction (e.g., stroke) or by stenting, as may symptoms that persist despite optimal medical management. In advanced centers, quite sophisticated manipulations, such as aortic stent graft reconstruction, realignment of true lumen flow, and fenestration, can be successfully accomplished. Traumatic aortic injuries (e.g., pseudoaneurysm, minimal intimal tear, flow-limiting lesions) are evaluated and perhaps better addressed with less morbidity than open surgical repairs. The same principle of endovascular stent graft repair often (but not invariably) is feasible for ruptured thoracic or abdominal aortic aneurysm. These IR procedures carry lower morbidity than invasive surgery and are usually possible, assuming that the anatomy is favorable and the procedure is undertaken emergently. Symptomatically, ischemic smaller vessels of the brain, extremities, and mesentery can also be stented effectively, assuming such preconditions are met.

**Venous Thrombosis**

IR has been rapidly developing a useful role for both submassive and massive venothrombosis. IR should be engaged early for consultation regarding catheter-based lytic infusions into the pulmonary artery or thrombectomy when standard medical management fails and/or systemic fibrinolysis is contraindicated. The appropriate place of temporary prophylaxis by IVC filter has been clarified recently but not entirely resolved (see below and Chapter 23). All but a few of the newer filtering devices are approved for permanent placement despite their option for catheter-based removal (Fig. 11-28). Most if not all of present day filters are MRI compatible. At least one of the latest filter options (VenaTech [B. Braun Interventional Systems Inc. Bethlehem, PA, USA]) is convertible over the short term from filtering to nonfiltering functions.

**FIGURE 11-28. One of many types of IVC filter (VenaTech).** After the high-risk period for embolism has passed, the core can be snared by its hook and removed. This allows the cage to remain permanently in place, acting as a stent rather than an occlusive obstruction.

With these improved features, the indications for IVC filters include patients with known VTE at high risk...
from anticoagulation and those failing such therapy. Perioperative patients with VTE or long bone and pelvic fractures often are candidates, as are those postendovascular thrombolysis/thrombectomy with residual deep vein thrombosis. Patients who are immobilized with precarious cardiopulmonary compensation who would not be expected to withstand recurrent embolism are often considered.

Interventional radiology now performs essential functions for early stroke (e.g., mechanical thrombectomy) and for intracranial hemorrhage evaluation and management. These services include diagnosis and treatment of vascular anomalies,

such as arteriovenous malformations and aneurysms. Small cerebral aneurysms may be coiled, and when timing and risk profiles are appropriate, carotid and intracerebral vascular stents may be considered to improve jeopardized perfusion of zones with critically compromised blood flow (Fig. 11-29).

![Diagram of cerebral aneurysm repair with stents and coils](image)

**FIGURE 11-29.** Two useful endovascular interventions for cerebral aneurysm repair: stenting and aneurysm obliteration by coils and clot.

Catheter-directed thrombolysis and/or percutaneous thrombectomy has gained increasing traction since the
introduction of sophisticated implements and safer drugs and dosing regimens for infusion. Full-intensity treatment can be directed to the point of interest with lower total anticoagulant doses while avoiding unneeded systemic overlap with its attendant risk. Lower doses avert an unacceptable bleeding risk. (Patients should not simultaneously receive a thrombolytic infusion and full dose anticoagulation.) Catheter-directed infusion therapy is a strong consideration for iliofemoral and caval venous clots as well as for life-threatening and symptomatic pulmonary emboli. The same strategy can be successfully applied to arterial occlusions occurring in circumstances of peripheral vascular disease or embolic, traumatic and iatrogenic compromise of extremities, mesentery, or brain.

![Figure 11-30](image)

**FIGURE 11-30.** Catheter inserted via left internal jugular vein could not be inserted into proper position for best function and safety (left). Fluoroscopic placement by IR repositioned the catheter to intended site (right). Arrows indicate catheter tip.

Percutaneous thrombectomy devices are diversifying and proliferating as their indications for use expand at a very rapid rate. Most devices rely on a suction removal mechanism with or without maceration. Such percutaneous procedures carry less morbidity risk than the more complex surgical interventions with which they compete (see Chapter 23).

**Vascular Access**

As critically ill patients often present challenges to achieve bedside vascular access (e.g., massive obesity, vasculopathy, recurrent instances of ICU care), the IR service is become highly valued for this purpose alone. IR practitioners are facile with US-guided cannula placement of central lines, cooling catheters, hemodialysis catheters, ports, and tunneled central venous lines. Misplaced catheters can also be repositioned with relative ease (Fig. 11-30). Arterial line access can usually be attained with relative ease.

**Management of Pseudoaneurysms**

Pseudoaneurysms may form due to trauma, infection, penetrating ulcer, or iatrogenic misadventure. Treatment of these depends upon location, etiology, and morphology. Infectious (mycotic) lesions generally require vascular surgery. On the other hand, IR is particularly well suited to address arterial site access anatomically amenable anomalies at the groin, where US-guided thrombin injection may be a good option. Large vessels may be appropriate for stent graft or embolization. Traumatic aortic injuries or transections may often be addressed by thoracic stent grafting. Worrisome vascular injuries and tangles in branch vessels of solid organs are generally approached by embolization. Larger feeding vessels are often stented.
Nonvascular Indications for IR

Nephrostomy tubes may be required to address renal obstruction, pyonephrosis, and/or urosepsis if urologic placement of a retrograde stent is not possible or desirable. Abdominal or pelvic drains may best be inserted and positioned radiographically under CT or US guidance. Follow-up imaging is very frequently indicated (e.g., abscessograms and fistula assessment). Complicated abscesses of the lung can be externally drained, but the commonly resulting bronchopleural fistula may require later surgical intervention, mandating early thoracic surgical consultation to choose the best treatment option. Similarly, though chest tubes are deftly placed into empyema pockets, an open surgical approach is sometimes a better option for complicated spaces. Early surgical consultation is again advised.

Tubes to drain pneumothorax tend to be better positioned, smaller, and more flexible when placed in IR using fluoroscopic or CT guidance, promoting patient tolerance (Fig. 11-31). Poorly functioning drainage tubes that serve any purpose (air/fluid/pus) can be replaced or repositioned in IR to optimize performance. After placement, decisions and management of drainage systems can be assigned to the interventional radiologist or to the bedside provider. This decision should be made at the time of tube insertion and followed through.

A variety of indications for IR involvement with tube placement relate to the GI tract. Cholecystostomy tube placement in IR is commonly a first-line intervention for the critically ill at prohibitively high risk for immediate cholecystectomy. Patients with acalculous cholecystitis may undergo initial drainage, with tube removal occurring 4 to 6 weeks later without the need for surgery at all, provided that the cystic and bile ducts are patent. Biliary drains are also commonly placed when obstruction cannot be effectively managed by endoscopy.
Percutaneous feeding tubes include gastrostomy (G tube) and gastrojejunostomy (GJ tube) variants. The former are placed to vent and drain the stomach and can be used for feeding. The latter may be more appropriate for patients predisposed to reflux and/or inclined to aspirate by gastric dysmotility or outlet obstruction. Insertion of nasal G and J tubes is often relegated to IR in patients in whom this cannot be successfully accomplished at the bedside, for those at unusually high risk for procedural problems or tissue trauma, and for those in whom appropriate tube placement must be unequivocally assured.

Other useful applications of IR services include pain management and suprapubic catheter placement to address bladder outlet obstruction that cannot be otherwise resolved by transurethral insertion. Challenging anatomy and failed attempts at lumbar puncture may sometimes prove successful under IR imaging guidance. Precise site localization before local anesthetic injection may be the only reasonable approach to such intractable pain problems as radiculopathy and abdominal pain addressable by celiac plexus block or ablation (e.g., secondary to
pancreatic carcinoma). Finally, intercostal blocks are effectively and safely performed by interventional radiology specialists.

**SUGGESTED READINGS**


Lichtenstein D. Novel approaches to ultrasonography of the lung and pleural space where are we now? *Breathe (Sheff).* 2017;13:100-111.


Chapter 12

Acid-Base Disorders

• Key Points

1. Viewed in isolation, most ABGs defy unique interpretation for cause or mandate immediate action; each blood gas must be evaluated in light of clinical information and electrolyte status. Good technique for blood gas sampling is important for accurate diagnosis.

2. During health, acid-base balance is finely tuned within a narrow range, using complex buffering systems and compensatory responses. Usually, the respiratory system responds quickly to metabolic derangements but ultimately achieves less complete compensation. By contrast, the kidney slowly compensates for respiratory abnormalities but eventually achieves and sustains a near-complete compensatory response.

3. The Stewart and Henderson-Hasselbalch approaches to acid-base evaluation use different systems to reach the same point (diagnosis). Using the adjusted anion gap (considering albumin concentration) improves the sensitivity of the classic approach to detect hidden acid-base disorders in hospitalized patients. Three major systems are of equal validity, differing only in how they approach understanding and analysis of the underlying mechanisms.

4. The rules of compensation for primary disturbances listed in Table 12-1 are important for the accurate evaluation of acid-base disorders. They should be memorized or kept closely at hand.

5. The anion gap and base excess provide valuable tools to determine whether a metabolic acidosis is the result of loss of bicarbonate or the result of titration of bicarbonate with excess hydrogen ion equivalents. It makes good sense to calculate the anion gap whenever evaluating electrolytes and ABGs. A short list of common conditions usually is responsible for elevating the anion gap (Table 12-3).

6. Hypoalbuminemia can mask an increased concentration of gap anions by lowering the value of the anion gap.

7. Non-anion gap acidosis often results from administration of large volumes of chloride-containing fluids. This occurs frequently in aggressive resuscitation with saline and in patients with GI losses of bicarbonate. Dilutional acidosis is observed when the patient is infused with high volumes of base-free solutions (e.g., sodium chloride), but the physiological consequences of this type of acidosis are rarely significant at the intracellular level.

8. The management of acid-base disorders requires comprehensive knowledge of the clinical setting. Bicarbonate correction of acidosis is appropriate in extreme cases where acidosis compromises hemodynamic status or when a depleted bicarbonate buffer base must be replenished. THAM, another effective buffer, has not been associated with the increase of intracellular acidosis that may occur during bicarbonate repletion and therefore may occasionally offer a useful alternative.

SYSTEMS USED TO ASSESS ACID-BASE STATUS

The earliest contemporary definitions of acid and base can be attributed to Arrhenius, who in 1887 defined acid as a hydrogen-ion donor and base as a hydroxyl ion donor. In 1948, Singer and Hastings proposed the concept of whole blood buffer base (BB) as a quantitative index of the surplus amount of fixed acid or base in the blood. In 1960, Astrup suggested that standard bicarbonate or base excess should be used as an index of the
nonrespiratory acid-base status of the blood. Standard bicarbonate is defined as the concentration of bicarbonate in plasma after fully oxygenated whole blood equilibrates with carbon dioxide at PCO$_2$ of 40 torr. The carbonic acid/bicarbonate system was introduced by Henderson-Hasselbalch, whose equation considers the pH to depend on the interactions of these variables. In 1983, the concept of buffer base was reintroduced by Stewart under the name "strong ion difference" (SID), based on simplifying principles of electroneutrality and mass conservation. Therefore, three related but different methods to analyze acid-base status are currently used: the Henderson-Hasselbalch relationship, the base excess, and the SID. To establish an accurate physiologic diagnosis and manage the different disturbances of acid-base balance requires integration of blood gas data with the electrolyte profile and clinical findings.

**ARTERIAL BLOOD GASES**

**Obtaining Arterial Blood Gases**

Arterial blood gases (ABGs) are valuable only if obtained properly and measured carefully. Patients should have a stable FiO$_2$ and ventilation status for at least 15 minutes before sampling to allow the PaO$_2$ and PaCO$_2$ to equilibrate. Patient position should be noted because PaO$_2$ may change significantly with varying body position (atelectasis and gas trapping are often worse in the supine position). Ventilatory pattern (breath-holding or hyperventilation) also should be noted. Changes in breathing rate or depth may significantly alter the PaCO$_2$ and PaO$_2$. Prolonged attempts to obtain an ABG often result in mild hyperventilation as pain and/or anxiety build. Body temperature should be recorded. For any given O$_2$ content, the measured PaO$_2$ increases as blood is warmed. An increased PaO$_2$ occurs because of rightward shifts in the oxyhemoglobin dissociation curve and because the solubility of gases decreases in warmer fluids, increasing their measurable tensions. Hypothermia shifts the oxyhemoglobin dissociation curve leftward; therefore, as cold blood is warmed to the standard analysis temperature (37°C), O$_2$ solubility decreases (resulting in a higher measured PaO$_2$ than exists in vivo). The PaCO$_2$ also will rise as blood is warmed, producing modest declines in the pH.

When sampling or cannulating the radial artery, it is advisable to assess collateral blood flow to the hand, as trauma to that vessel may later result in clotting and/or compromise its patency. The patency of the alternate blood supply, the ulnar artery, is confirmed by the Allen test, first described in 1929. It is performed by elevating the hand, occluding both ulnar and radial arteries, and releasing compression of the ulnar artery. If adequate collateral circulation is present, the hand should flush pink within 5 to 7 seconds. It is important to remember that the Allen test has high variability among observers, and its ability to detect inadequate collateral circulation is compromised in the hypotensive ICU population. Its performance must be considered, however, prior to placing a radial arterial catheter. For arterial puncture, the wrist is positioned in mild extension and the skin is cleaned—first with an iodophor or chlorhexidine solution and then wiped with alcohol. Lidocaine (approx. 0.5 mL of 1% solution) may be used to prevent pain in the alert subject. Excessive anesthetic volume may obliterate normal landmarks and arterial pulsations. Commercially prepared ABG syringes are usually used; however, in their absence, a heparin-coated 3-mL syringe tipped with a 21-gauge needle will suffice. The artery is approached from a 45-degree angle, and immediately on vessel entry, pulsatile blood will fill the syringe (aspiration is not necessary in most cases). Blood flow will cease if the needle penetrates the posterior arterial wall, but flow often may be reestablished merely by retracting the needle. After sampling is complete, the needle is removed and firm pressure should be applied to the puncture site for approximately 5 minutes (or longer if coagulation disorders exist). The blood and heparin should be mixed by a rolling motion between the fingers. Prompt analysis is required to obtain accurate results, and icing is needed unless the sample is analyzed immediately.
Pitfalls in Collection, Analysis, and Interpretation

**Timing of Analysis**
Accuracy depends on prompt analysis. Under most circumstances, the PaCO\textsubscript{2} rises approximately 3 to 10 mm Hg/h in uniced specimens, causing a modest fall in pH. The PaO\textsubscript{2} usually remains stable in an iced sample for 1 to 2 hours. Samples of body fluids that do not contain sufficient hemoglobin or other protein buffers (e.g., pleural or joint fluid) undergo more rapid pH changes when analysis is delayed.

**Pseudohypoxemia**
The PaO\textsubscript{2} may dramatically decrease if significant O\textsubscript{2} is consumed in vitro after the blood is sampled—a problem that is most common with marked leukocytosis or thrombocytosis. Leukocyte counts higher than 10\textsuperscript{5}/mm\textsuperscript{3} or platelet counts higher than 10\textsuperscript{6}/mm\textsuperscript{3} usually are required to produce significant changes. Addition of cyanide or immediate icing of the blood sample decreases the likelihood of this “pseudohypoxemia.” Diffusion of O\textsubscript{2} through the wall of plastic syringes may lead to analytical errors (particularly in samples with high O\textsubscript{2} tensions) because plastic syringes are much more permeable than glass to oxygen.

**Pseudoacidosis**
“Pseudoacidosis” may occur when metabolically active leukocytes generate large quantities of CO\textsubscript{2}, causing acidosis to develop in vitro. At room temperature, continued anaerobic glycolysis by red cells and white cells produces organic acids that can induce small reductions in pH and [HCO\textsubscript{3}\textsuperscript{-}] concentrations.

**Air Bubbles**
The PO\textsubscript{2} of room air at sea level is approximately 150 mm Hg, and the PCO\textsubscript{2} is near 0 mm Hg. Therefore, when large air bubbles are mixed with arterial blood, usually the PaO\textsubscript{2} rises and the PaCO\textsubscript{2} falls (if the PaO\textsubscript{2} in the blood exceeds that in the bubble; however, the measured PaO\textsubscript{2} could decline). A small air bubble in a relatively large sample has little effect, but when the ratio of bubble to blood volume is large, increases in PaO\textsubscript{2} of up to 30 mm Hg may occur. It is uncommon for bubbles to significantly reduce the PaCO\textsubscript{2} unless the baseline CO\textsubscript{2} tension is very high.

**Contamination of Arterial Samples with Venous Blood**
Normally, the PaCO\textsubscript{2} is higher, and PaO\textsubscript{2} is lower in venous blood than in arterial blood, as oxygen is extracted and carbon dioxide is added by metabolically active tissues. The degree of oxygen extraction varies greatly among organ systems. The heart is a near complete extractor of oxygen, whereas venous blood from the kidney contains large amounts of venous oxygen and less added CO\textsubscript{2}. Furthermore, the degree of O\textsubscript{2} extraction can vary substantially over time for any specific organ. This heterogeneity of venous O\textsubscript{2} tensions explains why a peripheral venous sample, predominately reflecting skin and muscle oxygen extraction, cannot serve as an accurate indicator of total body oxygen extraction or consumption.

**Arterial pH-Tissue pH**
It is not always correct to assume that arterial pH reflects the pH at the tissue level. Discordance is a particular problem in patients with severe circulatory failure, in whom pulmonary blood flow is substantially reduced. In this setting, blood that is delivered to the lungs may be adequately cleared of CO\textsubscript{2}, resulting in a relatively normal or
even diminished arterial PCO₂. However, the low cardiac output slows the return of CO₂-containing blood from the periphery. As a result, the mixed venous PCO₂, which represents blood that has not yet entered the pulmonary circulation, may be markedly higher than the PCO₂ in arterial blood.

**Risks of Arterial Blood Sampling**

Risks of arterial puncture are very low for single sticks but increase with frequency of access and when persistent cannulation is used (see Chapter 2). Infection is very rare unless infected tissue is traversed en route to the artery. Arterial thrombosis can usually be avoided by varying sampling sites, using the smallest needle that produces good blood flow and confirming collateral flow before puncture (approx. 3% of hospitalized patients have inadequate collateral circulation). Even when all appropriate precautions are taken, ischemic complications can occur as a result of thrombosis, systemic hypotension, vasopressor use, or underlying vascular disorder (e.g., Raynaud disease). Nerve trauma usually happens because of direct nerve puncture by an inexperienced or careless phlebotomist but also may result from a compressive hematoma if coagulopathy is present or if inadequate pressure is held at the puncture site.

**BASIC CONCEPTS OF ABG ANALYSIS AND INTERPRETATION**

Normally, arterial pH, the negative common logarithm of the hydrogen ion (H⁺) concentration, varies between 7.35 and 7.45. When breathing room air, normal PaCO₂ varies between 35 and 45 mm Hg, and PaO₂ values greater than 80 to 90 mm Hg are considered normal, depending on age. Mixed venous blood gases have a lower pH than arterial gases (normal, approx. 7.30 to 7.35), a lower PaO₂ (normal, approx. 40 to 44 mm Hg), and a slightly increased PaCO₂ (normal, approx. 45 mm Hg). Values for PaCO₂, PaO₂, and pH are measured directly. By contrast, the reported HCO₃⁻ concentration usually is not measured but rather is calculated from pH and PaCO₂, using a nomogram derived from the Henderson-Hasselbalch equation. In similar fashion, the reported arterial oxygen saturation (SaO₂) usually is not measured directly in the laboratory but calculated from the PaO₂.

**Alterations in Oxygenation**

**Oxygen Tension Versus Saturation**

At ambient pressure, oxygen content of blood is determined predominantly by the quantity of O₂ bound to hemoglobin (Hgb), with only a minor contribution from dissolved O₂. The O₂ carried in a volume of blood (mL/dL) is influenced by PaO₂ (mm Hg), Hgb concentration (g/dL), pH, and the characteristics of the Hgb itself: O₂ content = 1.34 (Hgb)(%Sat) + (0.003)(PaO₂). Normally, the quantity of dissolved oxygen is negligible, but it becomes significant when pure oxygen is administered under hyperbaric conditions. In such circumstances, PaO₂ can exceed 2,000 mm Hg, so that O₂ content increases appreciably by the dissolved oxygen. ABG analysis determines the partial pressure of dissolved O₂ directly but provides only an indirect (and often inaccurate) indicator of O₂ content.

**Hypoxemia**

Tolerance for hypoxemia depends not only on the extent of desaturation but also on the compensatory mechanisms available and the sensitivity of the patient to hypoxia. If an individual without cardiac limitation or anemia is made hypoxic over a short period of time, no important effect will be noted until PaO₂ falls below 50 to 60 mm Hg. At that level, malaise, light-headedness, mild nausea, vertigo, impaired judgment, and incoordination
generally are the first symptoms noted, reflecting the high sensitivity of cerebral tissue to hypoxia. Although minute ventilation increases, little dyspnea usually develops unless the resulting hyperpnea uncovers underlying mechanical lung problems, as in chronic obstructive pulmonary disease (COPD). Confusion resembling alcohol intoxication appears as PaO$_2$ falls into the range of 35 to 50 mm Hg, especially in older individuals with ischemic cerebrovascular disease (such patients also are prone to heart rhythm disturbances). As PaO$_2$ falls below 35 mm Hg, renal blood flow decreases, urine output slows, and atropine-refractory bradycardia and conduction system blockade develop. Lactic acidosis also appears at this level, even with normal cardiac function. The patient becomes lethargic or obtunded, and hypoxic drive to breathe is maximal. At a PaO$_2$ of approximately 25 mm Hg, the normal unadapted individual loses consciousness and minute ventilation begins to fall because of respiratory center depression. This sequence of events occurs at higher O$_2$ tensions if any of the major compensatory mechanisms for hypoxemia are defective. Even mild decreases in O$_2$ tension are tolerated poorly by anemic patients with impaired cardiac output or coronary insufficiency. Because the pulmonary vasculature constricts when alveolar O$_2$ tension falls, hypoxemia may provoke decompensation of the right ventricle in patients with preexisting pulmonary hypertension or cor pulmonale.

**Hyperoxia**

At normal barometric pressures, venous and tissue O$_2$ tensions rise very little when pure O$_2$ is administered to healthy subjects. Hence, nonpulmonary tissues are little affected. However, high concentrations of O$_2$ eventually replace nitrogen in the lung, even in poorly ventilated regions. Oxygen replacement of nitrogen eventually causes collapse of poorly ventilated units as O$_2$ is absorbed by venous blood faster than it is replenished. Atelectasis and diminished lung compliance result. More importantly, high O$_2$ tensions may accelerate the generation of noxious oxidants, injuring bronchial and parenchymal tissue. Although O$_2$-induced lung injury certainly occurs in healthy animals and promotes damage when high ventilating pressures are used, the susceptibility of already injured lungs to oxygen toxicity is much less certain.

**Alterations in Ventilation**

**Hypercapnia**

In addition to its key role in regulation of ventilation, the clinically important effects of CO$_2$ relate to changes in cerebral blood flow, pH, pulmonary artery pressure and adrenergic tone. Hypercapnia dilates cerebral vessels, and hypocapnia constricts them—a point of particular importance for patients with raised intracranial pressure. Acute increases in CO$_2$ depress consciousness, probably a combined result of intraneuronal acidosis, excessive cerebral blood flow, and rising intracranial pressure. Slowly developing hypercapnia is better tolerated, presumably because buffering has time to occur. The adrenergic stimulation that accompanies acute hypercapnia causes cardiac output to rise and helps maintain peripheral vascular resistance. Muscular twitching, asterixis, and seizures can be observed at extreme levels of hypercapnia in patients made susceptible by electrolyte or neural disorders.

As a practical matter, for mechanically ventilated patients, many practitioners permit a modest respiratory acidosis (pH of 7.10 to 7.20) resulting from gradual increases in PaCO$_2$ (<10 mm Hg/h) if the alternative is to markedly elevate airway pressures to achieve normocapnia. The practice of “permissive hypercapnia,” a consequence of using lower ventilating pressures and tidal volumes, has become widely accepted. Hypercapnia reduces tissue metabolism, improves surfactant function, and prevents nitration of proteins. Acidosis also decreases sarcoplasmic calcium release, dampens mitochondrial respiration, and reduces the activity of
enzymes that produce inflammatory metabolic intermediates. These changes favor adequate cellular functioning, control of inflammatory response, improved cardiac function, and maintenance or reactivation of hypoxic pulmonary vasoconstriction, with resultant improvement ventilation/perfusion matching.

**Hypocapnia**

The major effects of acute hypocapnia relate to alkalosis and diminished cerebral perfusion. Abrupt lowering of PaCO$_2$ reduces total cerebral blood flow, raises neuronal pH, and reduces available ionized calcium, causing disturbances in cortical and peripheral nerve function. Light-headedness, circumoral and fingertip paresthesias, and muscular tetany can result. Alkalosis caused by sudden reduction of PaCO$_2$ (e.g., shortly after initiating mechanical ventilation) can produce life-threatening seizures or arrhythmias.

**Evaluating Hydrogen Ion Concentration**

**Generation and Excretion of H$^+$ Ion**

Free H$^+$ ions are present in the body fluids in extremely low concentrations. However, H$^+$ ions are small and highly reactive, allowing them to bind more strongly than Na$^+$ or K$^+$ to negatively charged molecules. As a result, H$^+$ concentration is critical to the activity of cellular enzymes. Under normal conditions, the H$^+$ concentration varies little from the normal value of 40 nanoEq/L. The body buffers play an important role in this regulatory process, as they are able to take up or release H$^+$ ions to prevent large changes in the H$^+$ concentration. To keep H$^+$ within physiologic limits, generation and elimination rates must be equal. H$^+$ ion is normally generated in two ways:

1. By hydration of CO$_2$ to form “volatile” acid according to the reaction:

   \[ \text{CO}_2 + \text{H}_2\text{O} \Rightarrow \text{H}_2\text{CO}_3 \Rightarrow \text{H}^+ + \text{HCO}_3^- \]

2. By production of “fixed” acids (primarily sulfates and phosphates) as chemical by-products of metabolism

The kidneys and lungs play important roles in the maintenance of acid-base balance because they normally adjust the rate of acid excretion to meet homeostatic needs. Each day, approximately 15,000 mmol of CO$_2$ produced by endogenous metabolism is excreted by the lungs. Similarly, a normal diet generates 50 to 100 mEq of H$^+$ per day, derived mostly from the metabolism of sulfur-containing amino acids and the subsequent generation of H$_2$SO$_4$. These H$^+$ ions are initially buffered by HCO$_3^-$ and by the cellular and bone buffers to minimize the fall in extracellular pH. Acid-base balance is then restored by urinary H$^+$ excretion, which regenerates the HCO$_3^-$ lost in the original buffering reaction. If the H$^+$ concentration is increased, regardless of cause, it can be reduced toward normal by a decrease in the PCO$_2$ and/or an elevation in the plasma HCO$_3^-$ concentration. Both of these changes occur as alveolar ventilation and urinary excretion of H$^+$ are enhanced in this setting of acidosis. Conversely, alveolar ventilation and H$^+$ secretion diminish when the concentration of H$^+$ is reduced. The resultant increase in the PCO$_2$ and decline in the plasma HCO$_3^-$ concentration raise the H$^+$ concentration toward normal. If the excretion rate of fixed acid speeds or slows disproportionately in relation to its production rate, or if abnormal metabolic loads of acid or alkali develop, metabolic acidosis or alkalosis occurs. In clinical practice, the concentration of free H$^+$ ion is tracked by pH = -log [H$^+$].

**Base Excess**
The “base excess” is a calculated number that quantitates metabolic abnormality. It hypothetically “corrects” pH to 7.40 by first “adjusting” measured PaCO$_2$ to 40 mm Hg, thus allowing a comparison of the “corrected” $\text{HCO}_3^-$ with the known normal value at that pH (24 mEq/L). As a quick rule of thumb, base excess (mEq/L) can be calculated from the observed values for $\text{HCO}_3^-$ and pH:

$$\text{Base excess} = \text{HCO}_3^- + 10 (\text{pH} - 7.40) - 24.$$

A “negative” base excess means that $\text{HCO}_3^-$ stores are depleted. However, the base excess does not indicate whether retention or depletion of $\text{HCO}_3^-$ is pathologic or compensatory for long-standing respiratory derangements; that judgment must be made by an analysis of the clinical setting. Likewise, it does not dictate the need for bicarbonate administration. Calculation of base excess is especially helpful when the observed $\text{HCO}_3^-$ is nearly normal (24 ± 3 mEq/L). The base excess calculation is unlikely to provide new insights at more extreme $\text{HCO}_3^-$ deviations but nonetheless is useful in gaging the severity, progress, and prognosis of acute critical illness.

**Buffer Systems**

**Carbonic Acid**

Chemical and protein buffer systems oppose changes in free H$^+$. The CO$_2$/$\text{HCO}_3^-$ (carbonic acid) and hemoglobin systems are quantitatively the most important. Clinical attention usually is focused on the carbonic acid system because each of its components is measured readily and because CO$_2$ and $\text{HCO}_3^-$ determinations allow clinical judgments to be made concerning the respiratory or metabolic origin of the problem at hand. To maintain pH at 7.40, the ratio of $\text{HCO}_3^-$ to (0.03 × PaCO$_2$) must remain in the 20:1 proportion dictated by the Henderson-Hasselbalch equation:

$$\text{pH} = 6.1 + \log \left[ \frac{\text{HCO}_3^-}{(0.03 \times \text{PaCO}_2)} \right]$$

**Noncarbonic (Protein) Buffers**

Noncarbonic buffers may be intracellular or extracellular and include proteins (albumin, hemoglobin), phosphates, and bone carbonates. On average, 55% to 60% of an acid load will eventually be buffered by the cells and bone, although even higher percentages may occur with severe acidemia when extracellular $\text{HCO}_3^-$ stores are markedly reduced. Noncarbonic buffers bind or release H$^+$ ions, minimizing pH changes while allowing the hydration reaction for CO$_2$ to continue to run in either direction.

$$\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow [\text{H}^+] + \text{HCO}_3^-$$

$$\downarrow$$

$$[\text{H}^+] + \text{Hgb} \leftrightarrow \text{H}^+\text{Hgb}$$

For this reason, if PaCO$_2$ changes acutely, there will be a small associated change in $\text{HCO}_3^-$ in the same direction (approx. 1 mEq/L per 0.1 pH unit). Such automatic changes in $\text{HCO}_3^-$ do not imply a metabolic disturbance, and the base excess attributable to this mechanism is zero. Anemic blood fails to buffer fluctuations...
in H⁺ concentration with normal efficiency.

**Compensatory Mechanisms**

As physiologic stresses on pH balance persist, adjustments in the excretion rate of CO₂ and H⁺ counterbalance the effect of these disturbances on pH. In general, renal compensation for a respiratory disturbance is slower (but ultimately more successful) than respiratory compensation for a metabolic disturbance. Thus, although quick to respond initially, the respiratory system will not eliminate sufficient CO₂ to completely offset any but the mildest metabolic acidosis. Furthermore, the respiratory compensatory response is not developed fully until 24 to 48 hours after initial activation. The lower limit of sustained compensatory hypocapnia in a healthy adult is approximately 10 to 15 mm Hg. Once that limit is reached, even small additional increments in H⁺ ion have exaggerated effects on pH.

Patients with disordered lung mechanics, such as those with COPD or neuromuscular weakness, are highly vulnerable to metabolic acid loads because they lack the normal ability to compensate by hyperventilation. CO₂ retention in response to alkalosis is very limited—only rarely exceeding 60 mm Hg. Moreover, the hypoxemia resulting from hypoventilation helps limit the rise in CO₂ by eventually triggering increased ventilatory effort. Although the kidney cannot respond effectively to abrupt respiratory acidosis or alkalosis, renal compensation may eventually (3 to 7 days) totally counterbalance a respiratory alkalosis of even moderate severity. The kidney also compensates well for chronic respiratory acidosis but cannot compensate completely for a PaCO₂ above 65 mm Hg unless another stimulus for HCO₃⁻ retention (e.g., volume depletion) is present.

**Role of Electrolytes in Acid-Base Balance**

According to the principle of maintained electroneutrality, the number of positive and negative charges in body fluids must be equal. Accordingly, serum cations (sodium + potassium + calcium + magnesium) must equal anions (chloride + bicarbonate + proteins [e.g., albumin] + sulfate + phosphate + organic acid anions). The balance among these electrolytes influences acid-base status (see anion gap and Stewart Approach). In fact, evaluation of acid-base status is incomplete without consideration of the clinical setting and the electrolyte profile.

**ACID-BASE DERANGEMENTS**

**Terminology of Acid-Base Disorders**

The terms *acidemia* and *alkalemia* refer to blood pH. Systemic pH lower than 7.35 defines acidemia. A pH higher than 7.45 defines alkalemia. By contrast, acidosis and alkalosis do not refer to pH but rather to basic pathophysiologic processes or tendencies favoring the development of acidemia or alkalemia. For example, a patient with diabetic ketoacidosis (DKA) (a primary metabolic acidosis) and hypocapnia stimulated by pneumonia (a primary respiratory alkalosis) may exhibit acidemia, alkalemia, or a normal pH depending on the relative changes in PaCO₂ and HCO₃⁻. Uncomplicated metabolic acidosis is characterized by a decline in HCO₃⁻, whereas a primary increase in HCO₃⁻ denotes metabolic alkalosis. Conversely, respiratory acidosis is defined as a primary increase in PaCO₂, whereas respiratory alkalosis occurs when the central feature is a decrease in PaCO₂.

**Stepwise ABG Analysis**

We can use one or both of the following approaches to characterize the acid-base status.
*Henderson-Hasselbalch Approach*

Because no set of ABG values has a unique interpretation, concomitant analysis of serum electrolytes and the review of the clinical situation are essential to reach the correct diagnosis in an acid-base disorder. Three specific factors (pH, PaCO₂, and the ratio of PaCO₂ to \(\text{HCO}_3^-\)) must be evaluated in a logical stepwise fashion. Interpretation of the pH and PaCO₂ rapidly provides a definitive diagnosis in most cases. The remaining disorders can be classified by examining the relationship of the measured PaCO₂ to the PaCO₂ expected, based on the measured bicarbonate level. Consideration of the anion gap often lends supportive information.

The pH is analyzed first. Values below the normal range indicate acidemia (elevated H⁺). A pH value above the normal range (reduced H⁺) defines alkalemia. A pH within the normal range has three possible interpretations: (1) no acid-base disorder exists; (2) two or more acid-base disorders with perfectly offsetting pH effects exist (rare); or (3) near-complete physiologic compensation has occurred for one or more primary disorders. Deviations of pH from normal usually are quickly acted on by compensatory mechanisms in an attempt to restore the pH to a normal value. When the primary disorder is respiratory, the kidney attempts to compensate. When metabolic consumption or wasting of buffer base is the primary problem, the lung attempts to return the pH to normal.

In the acidemic patient, an elevated PaCO₂ indicates that some component of respiratory acidosis is present. In such patients, the bicarbonate concentration can be used to decide whether appropriate metabolic compensation is occurring or if a concurrent metabolic disorder is present. If the measured \(\text{HCO}_3^-\) concentration has increased over baseline by 0.10 to 0.35 units for each 1-mm Hg change in PaCO₂, appropriate metabolic compensation for a respiratory acidosis is taking place. Lesser increases in \(\text{HCO}_3^-\) are indicative of a complicating metabolic acidosis or suggest that insufficient time has elapsed for the kidney to compensate for the rapidly changing PaCO₂. Greater rises in \(\text{HCO}_3^-\) indicate a superimposed metabolic alkalosis.

Conversely, a reduced PaCO₂ in an acidemic patient indicates metabolic acidosis. In the case of a metabolic acidosis, the ultimate diagnosis is reached by comparing the observed PaCO₂ to that predicted by directly measuring the serum \(\text{HCO}_3^-\) content. For any given \(\text{HCO}_3^-\) value, the expected PaCO₂ = (1.5 × \(\text{HCO}_3^-\)) + (8 ± 2). This equates to roughly a 1.0- to 1.3-mm Hg change in PaCO₂ for each mEq change in bicarbonate.

Typically, respiratory compensation for a metabolic acidosis is more rapid but less complete than the converse. If the observed PaCO₂ equals the expected value, a simple metabolic acidosis with appropriate respiratory compensation is present. If the PaCO₂ exceeds the expected value, the patient has both a respiratory and metabolic acidosis. If the PaCO₂ fails to reach the expected level, components of both metabolic acidosis and respiratory alkalosis may exist.

In the alkalemic patient, a low PaCO₂ diagnoses respiratory alkalosis. Determination of whether the disorder is simple or mixed results from examining a concurrently measured \(\text{HCO}_3^-\) concentration.

Reductions in \(\text{HCO}_3^-\) concentration of 0.2 to 0.5 times the change in PaCO₂ will occur slowly to provide the compensation necessary. Failure to lower \(\text{HCO}_3^-\) by at least 0.2 times the change in PaCO₂ suggests a superimposed metabolic alkalosis (or insufficient compensatory time), whereas a \(\text{HCO}_3^-\) that declines by more than 0.5 times the change in PaCO₂ suggests a component of metabolic acidosis (Table 12-1).
### Table 12-1. Expected Compensation for Acid-Base Disorders

<table>
<thead>
<tr>
<th>Primary Disorder</th>
<th>Primary Change</th>
<th>Compensatory Change</th>
<th>Expected Compensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>↓ HCO$_3^-$</td>
<td>↓ PaCO$_2^2$</td>
<td>$\Delta$PaCO$_2^2$ = 1.2 $\Delta$HCO$_3^-$</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>↑ HCO$_3^-$</td>
<td>↑ PaCO$_2^2$</td>
<td>$\Delta$PaCO$_2^2$ = 0.9 $\Delta$HCO$_3^-$</td>
</tr>
<tr>
<td>Respiratory acidosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>↑ PaCO$_2^2$</td>
<td>↑ HCO$_3^-$</td>
<td>$\Delta$HCO$_3^-$ = 0.10 $\Delta$PaCO$_2^2$</td>
</tr>
<tr>
<td>Chronic</td>
<td></td>
<td></td>
<td>$\Delta$HCO$_3^-$ = 0.35 $\Delta$PaCO$_2^2$</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>↓ PaCO$_2^2$</td>
<td>↓ HCO$_3^-$</td>
<td>$\Delta$HCO$_3^-$ = 0.2 $\Delta$PaCO$_2^2$</td>
</tr>
<tr>
<td>Chronic</td>
<td></td>
<td></td>
<td>$\Delta$HCO$_3^-$ = 0.5 $\Delta$PaCO$_2^2$</td>
</tr>
</tbody>
</table>

The ultimate diagnosis of the alkalotic patient with an elevated PaCO$_2^2$ is made by comparing the measured PaCO$_2^2$ value with that expected (calculated), based on the measured serum HCO$_3^-$ concentration. In the presence of a simple compensated metabolic alkalosis, the expected PaCO$_2^2$ = (0.7 × HCO$_3^-$) + (20 ± 1.5). A higher observed PaCO$_2^2$ indicates the presence of a simultaneous respiratory acidosis. A PaCO$_2^2$ value lower than expected indicates a concomitant respiratory alkalosis.

**Stewart Approach (Strong Ion Difference)**

In 1983, Peter Stewart published his modern quantitative approach to acid-base chemistry. According to his interpretation, the traditional concepts of the mechanisms behind the changes in acid-base balance are questionable. The main physicochemical principles that must be satisfied are the rule of electroneutrality (mentioned previously) and the principle of mass conservation. Three components in biological fluids are subjected to these principles: (1) water, which is only weakly dissociated into H$^+$ and OH$^-$; (2) strong ions, completely dissociated electrolytes such as Na$^+$, K$^+$, Cl$^-$, and certain molecules or compounds, such as lactate (strong ions cannot be created or destroyed to satisfy electroneutrality, but H$^+$ ions can be generated or consumed by changes in water dissociation to establish this required electroneutrality balance); and (3) weak acids, incompletely dissociated compounds. Stewart strictly distinguished between dependent and independent variables in accord with these principles. The three dependent variables (bicarbonate, pH, and H$^+$ concentrations) can only change if the three independent variables allow this change. These three independent variables are PCO$_2$, the total amount of all weak acids ([A$^-$] called $A_{TOT}$), and the SID.

$A_{TOT}$ can be calculated from the concentration of the albumin (Alb) and the phosphate concentration (Pi):
An apparent SID can be calculated using measurable ion concentrations:

$$A_{Tot} = [Alb(0.123 \times pH - 0.631)] + [Pi(0.309 \times pH - 0.469)]$$

But a simpler formula is

$$\text{SID}_a = (\text{Na} + \text{K} + \text{Ca} + \text{Mg}) - (\text{Cl} + \text{lactate})$$

In healthy humans, the normal SID is 40 to 42 mEq/L. Regarding metabolic disturbances of acid-base chemistry, changes in pH, $\text{H}^+$, and $\text{HCO}_3^-$ are only possible if either SID or $A_{TOT}[A']$ changes. If, for example, SID decreases (e.g., in case of hyperchloremia), this increase in "independent" negative charges leads to a decrease in "dependent" negative charges ($\text{HCO}_3^-$), resulting in acidosis (and vice versa). In other words, SID less than 40 mEq/L implies metabolic acidosis. According to Stewart, the decrease in SID during hyperchloremic acidosis results from the increase in serum chloride concentration and is the causal mechanism behind this acidosis. As another example, a decrease in independent weak acids [A'] (e.g., during hypoalbuminemia) leads to an increase in dependent $\text{HCO}_3^-$, a subsequent increase of SID, and alkalosis.

An SID greater than 42 mEq/L indicates metabolic alkalosis. By Stewart approach, new types of acid-base disturbance, such as "hyperchloremic acidosis" or "hypoalbuminemic alkalosis" (which, of course, can also exist in combination), have been identified that had gone unrecognized by the classic acid-base analysis. Consequently, Stewart analysis complements the understanding of the mechanisms behind the changes in acid-base balance.

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Both methods, $\text{HCO}_3^-/\text{PaCO}_2$ and SID, yield virtually identical results when used to quantify the acid-base status of a given blood sample and clinical condition.

**SIMPLE ACID-BASE DISORDERS**

**Metabolic Acidosis**

**Mechanisms**

Metabolic acidosis is the consequence of one of four basic mechanisms: bicarbonate consumption from decreased $\text{H}^+$ excretion, bicarbonate consumption from increased $\text{H}^+$ production, bicarbonate loss, and bicarbonate dilution (Table 12-2).

<table>
<thead>
<tr>
<th>Table 12-2. Etiology of Metabolic Acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INABILITY TO SECRETE THE DIETARY ACID LOAD</strong></td>
</tr>
<tr>
<td>1. Diminished $\text{NH}_4^+$ production</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Hypoaldosteronism (type IV renal tubular acidosis)</td>
</tr>
</tbody>
</table>
INCREASED H⁺ LOAD OR \( \text{HCO}_3^− \) LOSS

1. Lactic acidosis
2. Ketoacidosis
3. Ingestions
   - Salicylates, methanol or formaldehyde, ethylene glycol, paraldehyde, toluene, ammonium chloride, sulfur, and hyperalimentation fluids
4. Massive rhabdomyolysis
5. Gastrointestinal \( \text{HCO}_3^- \) loss
   - Diarrhea
   - Pancreatic, biliary, or intestinal fistulas
   - Ureterosigmoidostomy
   - Cholestyramine
6. Renal \( \text{HCO}_3^- \) loss
   - Type II (proximal) renal tubular acidosis

DILUTIONAL ACIDOSIS

Bicarbonate Consumption

H⁺ normally is excreted renally as titratable acid (phosphates and sulfates) and as ammonia compounds. Renal failure, adrenal insufficiency, distal renal tubular acidosis (RTA), and hypoaldosteronism impair this excretion. Patients with renal failure owing to a reduced number of functioning nephrons cannot adequately filter and excrete the H⁺ load. In distal (type I) RTA, proximal tubular glomerular filtration and \( \text{HCO}_3^- \) reabsorption are normal, but distal tubular H⁺ secretion is impaired. Because H⁺ excretion in the distal tubule depends on exchange of sodium ions, volume depletion worsens the tendency for acidosis. Through a similar mechanism (reduced tubular sodium delivery), adrenal insufficiency or selective hypoaldosteronism also impairs H⁺ excretion. The latter condition may be recognized by the association of metabolic acidosis, hyperkalemia, hyponatremia, and hypercalcemia.

Hydrogen Ion Load and the Anion Gap

An increased H⁺ load also may cause metabolic acidosis. In such cases, the disparity between the measured concentrations of serum cations and anions—the anion gap—will widen beyond the normal range. These normally hidden anions are composed of serum proteins (predominantly albumin), phosphate, sulfate, lactate, ketoacids (beta hydroxybutyrate, acetoacetate), and other compounds (e.g., drugs).

The anion gap is based on the principle of electroneutrality mentioned previously. The simplified formula is:

\[
\text{AG} = (\text{Na}^+) - (\text{HCO}_3^- + \text{Cl}^-)
\]

The anion gap has traditionally been simplified and measured as the serum sodium concentration minus the sum of the bicarbonate and chloride concentrations because the potassium concentration is a small quantity that varies only slightly. The normal value for the anion gap ranges from 8 to 12 mmol/L, is dependent of the type of analyzer used, and must be established for each laboratory separately.

The serum anion gap has been proposed to be useful in three clinical settings. The presence or absence of anion gap offers invaluable help in determining the cause of metabolic acidosis. Thus, metabolic acidosis with an increased anion gap is usually attributable to disorders associated with the accumulation of either endogenous
or exogenous organic acids (methanol, ethylene glycol, salicylate). The magnitude of the increase in the anion gap is important. With an anion gap more than 15 mmol/L, an organic acidosis is nearly always present. However, mild increases in the anion gap may be relatively insensitive for detecting the presence of mild to moderate organic acidosis, such as the lactic acidosis encountered in critically ill patients (Table 12-3). As a rule, the larger the anion gap, the easier it is to determine the cause of the acidosis. A wide anion gap acidosis usually can be diagnosed rapidly with a clinical history and a limited number of serum tests (i.e., serum creatinine, lactate, and ketone levels). Lactic acidosis generated by anaerobic glycolysis is the most common cause of an elevated anion gap; however, lactic acidosis often is mixed with another form of acidosis. For example, very high serum levels of anionic salicylate molecules may directly elevate the anion gap, but salicylates also raise the anion gap by interfering with carbohydrate metabolism and O₂ utilization, thereby inducing a lactic acidosis. Similarly, DKA produces a mixed anion gap metabolic acidosis by increasing the concentration of unmeasured ketones and by inducing a lactic acidosis, usually from hypoperfusion (see Chapter 32). Uremia commonly leads to accumulation of titratable acids, producing an anion gap metabolic acidosis.

Table 12-3. Anion Gap and Metabolic Acidosis

<table>
<thead>
<tr>
<th>HIGH ANION GAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lactic acidosis: D-lactate</td>
</tr>
<tr>
<td>2. Ketoacidosis: β-hydroxybutyrate</td>
</tr>
<tr>
<td>3. Renal failure: sulfate, phosphate, urate, hippurate</td>
</tr>
<tr>
<td>4. Ingestions</td>
</tr>
<tr>
<td>5. Massive rhabdomyolysis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NORMAL ANION GAP (HYPERCHLOREMIC ACIDOSIS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Gastrointestinal loss of $\text{HCO}_3^-$</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>2. Renal $\text{HCO}_3^-$ loss</td>
</tr>
<tr>
<td>Type II (proximal) renal tubular acidosis</td>
</tr>
<tr>
<td>3. Renal dysfunction</td>
</tr>
<tr>
<td>Some cases of renal failure</td>
</tr>
<tr>
<td>Hypoaldosteronism (type IV renal tubular acidosis)</td>
</tr>
<tr>
<td>Type I (distal) renal tubular acidosis</td>
</tr>
<tr>
<td>4. Ingestions</td>
</tr>
<tr>
<td>Ammonium chloride</td>
</tr>
<tr>
<td>Hyperalimentation fluids</td>
</tr>
<tr>
<td>5. Some cases of ketoacidosis, particularly during treatment with insulin</td>
</tr>
</tbody>
</table>

If the creatinine, ketone, and lactate levels are all normal in the setting of a high anion gap, a toxic ingestion
becomes the most likely etiology. In such patients, comparing the calculated osmolality to measured serum osmolality proves particularly helpful. An osmolal gap usually indicates some form of alcohol toxicity: ethylene glycol, ethanol, or methanol. Other drugs that can cause an anion gap acidosis include isoniazid, iron, and paraldehyde (see Chapter 33).

The second setting in which the anion gap may be useful occurs when ascertaining if a mixed acid-base disturbance is present. Here the anion gap is a component of the “Delta Ratio” or “Δ/Δ,” defined as the change in the anion gap divided by the change in the serum bicarbonate. The delta ratio is sometimes used in the assessment of elevated anion gap metabolic acidosis to determine if a mixed acid base disorder is present.

\[
\text{Delta ratio} = \frac{\Delta \text{Anion gap}}{\Delta \text{HCO}_3^-} = \frac{(AG_{\text{observed}} - AG_{\text{expected}})}{(\text{HCO}_3^-_{\text{observed}} - \text{HCO}_3^-_{\text{expected}})}
\]

This calculation is based on the principle that each milliequivalent of acid added to the body should reduce the serum bicarbonate by an equivalent amount. Therefore, when the Delta in the anion gap is larger than the Delta in the serum bicarbonate (Δ/Δ > 1), this implies an additional source of base (metabolic alkalosis). In other words, if the magnitude of decrease in bicarbonate is less than the magnitude of increase in anion gap, then more base than expected has been added, suggesting an associated alkalotic process.

If all the dissociated acid in the extracellular fluid (ECF) and all the buffering were by bicarbonate, then the increase in the anion gap (AG) should equal the decrease in bicarbonate so the ratio between these two changes (the delta ratio) should equal one. As described previously, however, considerable buffering occurs intracellularly and by bone, not by \[^{3}\text{HCO}_3^-\]. Most of excess anions remain in the ECF because anions cannot easily cross the lipid bilayer of the cell membrane. As a result, the elevation in the anion gap usually exceeds the fall in the plasma \[^{3}\text{HCO}_3^-\]. In lactic acidosis, for example, the Δ/Δ ratio averages 1.6:1. On the other hand, even though the same principle applies to ketoacidosis, the ratio is usually closer to 1:1 in this disorder because the loss of urinary ketoacid anions (ketones) lowers the anion gap and tends to balance the effect of intracellular buffering. Anion loss in the urine is much less prominent in lactic acidosis because the associated state of marked tissue hypoperfusion usually results in little or no urine output.

A value above 2:1 indicates a lesser fall in \[^{3}\text{HCO}_3^-\] than one would expect, given the change in the anion gap. This can be explained by another process that increases the \[^{3}\text{HCO}_3^-\], that is, a concurrent metabolic alkalosis. Another situation to consider when the delta ratio exceeds 2 is a high preexisting \[^{3}\text{HCO}_3^-\] level, as would be seen in chronic respiratory acidosis. It should be appreciated that hydrogen buffering in cells and bone takes several hours to complete. Thus, the ratio may be close to 1:1 with very acute lactic acidosis (seizures or exercise to exhaustion) because there has not been time for nonextracellular buffering to occur.

When the change in the anion gap is less than that in the serum bicarbonate concentration (Δ/Δ < 1), this implies an additional source of acid (non-anion gap metabolic acidosis). In other words, more bicarbonate has been consumed than expected, and it may be explained by addition of other source of acid, suggesting an associated non-anion gap acidotic process. However, this assumption applies only when the proton and its conjugate base have the same volume of distribution. But as described earlier, more than 50% of the excess H\(^+\) is buffered by the cells and bone, not by \[^{3}\text{HCO}_3^-\]. By contrast, most of the excess anions remain in the ECF because their distribution is pH dependent. A delta-delta value less than 1:1 indicates a greater fall in \[^{3}\text{HCO}_3^-\] than one would expect, given the increase in the anion gap. This can be explained by a mixed metabolic acidosis, that is, a combined elevated anion gap acidosis and a normal anion gap acidosis, as might occur when lactic acidosis is
superimposed on severe diarrhea. In this situation, the additional fall in $\text{HCO}_3^-$ is due to further buffering of an acid that does not contribute to the anion gap (i.e., addition of HCl to the body as a result of diarrhea).

In summary, the $\Delta/\Delta$ ratio is normally between 1 and 2 in patients with an uncomplicated high anion gap metabolic acidosis. A value below 1:1 suggests a combined high anion gap acidosis and normal anion gap acidosis, as might occur when hemoconcentration and lactic acidosis are superimposed on severe diarrhea. On the other hand, a value above 2:1 suggests that the fall in the plasma $\text{HCO}_3^-$ concentration is less than expected because of a concurrent metabolic alkalosis.

The third setting in which the anion gap may be useful is in detecting selected disorders that occur when the anion gap is low, rather than high. A low anion gap can occur with a decrease in unmeasured anions, as in hypoalbuminemia. Hypoalbuminemia, a common disturbance in hospitalized patients, can mask an increased concentration of gap anions by lowering the value of the anion gap. For example, in a diabetic patient with hypoalbuminemia, significant ketoacidosis can be missed if ketones are not directly measured. The observed anion gap can be adjusted for abnormal albumin concentration, by considering that each g/L decrease in serum albumin causes the observed anion gap to underestimate anion gap by 0.25 mEq/L.

$$\text{Adjusted anion gap} = \text{observed anion gap} + 0.25 \times (\text{normal albumin} - \text{observed albumin})$$

where albumin concentrations are in g/L. (If given in g/dL, the factor is 2.5.)

A low anion gap may be observed if there is an increase in unmeasured cations, as in lithium intoxication, or in cases of multiple myeloma in which cationic paraproteins are produced. Rarely, the anion gap may actually be negative, as in severe hyperlipidemia or bromide intoxication. In such rare situations, adjusting for hypoalbuminemia does not correct this aberrancy.

**Bicarbonate Loss**

Bicarbonate loss may produce metabolic acidosis but does not elevate the anion gap because $\text{HCO}_3^-$ loss results in compensatory hyperchloremia. Although renal failure usually impairs $\text{H}^+$ excretion, renal failure may also induce direct $\text{HCO}_3^-$ loss. In renal failure, the $\text{HCO}_3^-$ usually plateaus at 12 to 20 mmol/L, as further $\text{H}^+$ accumulation is blunted by tissue (bone) buffers. Three conditions decrease $\text{HCO}_3^-$ disproportionately to reductions in glomerular filtration rate: renal medullary tubular disorders (e.g., proximal RTA), low renin/aldosterone states, and renal failure, in which there is decreased $\text{HCO}_3^-$ reabsorption (because of a constant filtered Na$^+$ load and an increased filtration fraction through the few remaining nephrons). The mild metabolic acidosis of proximal (type II) RTA usually is an incidental finding resulting from an inability to fully resorb filtered $\text{HCO}_3^-$ in this usually self-limited disease, the impaired reabsorptive capacity for $\text{HCO}_3^-$ renders pH correction difficult and produces an alkaline urine. In such patients, exogenous NaHCO$_3$ increases the filtered $\text{HCO}_3^-$ load, and raises urinary pH, but seldom affects serum pH. In addition to metabolic acidosis and alkaline urine, ancillary features characteristic of proximal RTA are as follows: decreased serum urate, $\text{HCO}_3^-$, and potassium, aminoaciduria, and glycosuria.

The gastrointestinal (GI) tract frequently provides a route for $\text{HCO}_3^-$ loss in patients with chronic diarrhea. Diarrhea related to human immunodeficiency virus (HIV) or laxative abuse is relatively common. In such patients, urinary pH can be a helpful diagnostic test—a normal kidney will increase acid excretion (and reclaim $\text{HCO}_3^-$),
resulting in a urine pH lower than 5.0. Because the ileum and colon have ion pumps that exchange $\text{HCO}_3^-$ and $\text{Cl}^-$, hyperchloremic (nongap) acidosis frequently develops in patients with ureterosigmoidostomy.

**Dilutional Acidosis**

This type of acidosis is observed mainly when a high volume of saline solution has been given. The simplest explanation for dilutional acidosis from a physicochemical point of view is that admixture of large volumes of a solution less alkaline than blood, such as saline (which contains no bicarbonate), will result in less alkalinity (i.e., more acidity of the solution). Because most body metabolism is performed intracellularly and there is no practical method to obtain intracellular samples, we sample the blood and often presume that it reflects intracellular acid-base kinetics. However, the acidosis resulting from normal saline infusion does not reflect an intracellular metabolic derangement. For the same degree of acidemia, a dilutional acidosis might be expected to be less worrisome than a metabolic acidosis caused by an intracellular metabolic derangement for at least two reasons. First, there is no underlying metabolic derangement associated with simple dilutional acidosis. Second, for the same degree of acidemia, the initial pH change in the dilutional acidosis occurs extracellularly, and a lesser or delayed pH change occurs intracellularly. Conversely, in the metabolically deranged patient, the initial pH change occurs intracellularly and a lesser or delayed change occurs extracellularly.

**Urine Anion Gap**

Calculation of the urine anion gap may be helpful diagnostically in some cases with a normal anion gap metabolic acidosis. The major measured cations and anions in the urine are $\text{Na}^+$, $\text{K}^+$, and $\text{Cl}^-$; thus, the urine anion gap is

\[
\text{Urine anion gap} = (\left[\text{Na}^+ + \text{K}^+\right] - \left[\text{Cl}^-\right]) - \text{Unmeasured cations} - \text{Unmeasured anions}
\]

In normal subjects excreting between 20 and 40 mEq of $\text{NH}_4^+$ per liter ($\text{NH}_4^+$ being the major unmeasured urinary cation), the urinary anion gap (UAG) generally has a positive value or is near zero. In metabolic acidosis, however, the excretion of $\text{NH}_4^+$ (and of $\text{Cl}^-$ to maintain electroneutrality) should increase markedly if renal acidification is intact, resulting in a UAG value that varies from -20 to more than -50 mEq/L. The negative value in this setting occurs because in keeping with the principle of electroneutrality, the $\text{Cl}^-$ now exceeds the sum of $\text{Na}^+$ plus $\text{K}^+$. In comparison, the acidemia in renal failure and Types I and IV RTA are primarily due to impaired $\text{H}^+$ and $\text{NH}_4^+$ excretion, causing the UAG to retain its normally positive value.

There are two conditions in which the urine anion gap cannot be used. The first is a high anion gap acidosis, such as ketoacidosis, where the excretion of unmeasured ketoacid anions in the urine will counteract the effect of $\text{NH}_4^+$. The second is volume depletion with avid Na$^+$ retention (urine sodium < 25 mEq/L). The associated decrease in distal Na$^+$ delivery impairs distal acidification, and the associated increase in Cl$^-$ reabsorption prevents the excretion of NH$_4$Cl. Volume depletion represents a reversible form of type I RTA, despite the development of a negative anion gap.

**Signs and Symptoms**

Unlike those with respiratory acidosis, patients with metabolic acidosis usually have an increased depth and rate of respiration unless ventilatory drive is depressed. If the acidosis is severe, lethargy or coma may occur. Neurologic changes are less prominent with metabolic than with respiratory acidosis, perhaps because the hypercapnia and hypoxemia of
respiratory acidosis exert independent effects and because intracerebral pH may be considerably lower, because of easier movement of CO$_2$ across the blood-brain barrier. Moderate to severe metabolic acidosis may decrease blood pressure, depress heart function, alter the effects of catecholamines on the cardiovascular system, and impair smooth muscle function, leading to such complications as gastroparesis, emesis, and regurgitation of gastric contents.

**Compensation**

There are several compensatory mechanisms for metabolic acidosis. Initially, extracellular buffers (predominantly HCO$_3^-$) blunt the falling pH. Rapidly thereafter, the metabolic acidosis stimulates both the central and peripheral chemoreceptors controlling respiration, increasing alveolar ventilation to reduce PaCO$_2$, and raising the extracellular pH toward normal. The increase in ventilation begins within 1 to 2 hours and reaches its maximum level at 12 to 24 hours. Hyperpnea is characterized more by an increase in tidal volume than by an increase in respiratory rate and may, if the acidemia is severe, reach values exceeding 30 L/min. This degree of hyperventilation (called Kussmaul respiration) is usually apparent on physical examination and should alert the physician to a possible underlying metabolic acidosis. The PaCO$_2$ declines at a rate of approximately 1.2 mm Hg/mEq/L reduction in serum HCO$_3^-$ but rarely falls below 10 mm Hg. The PaCO$_2$ expected in response to an established metabolic acidosis may be predicted from the following equation: expected PaCO$_2$ = 1.5 x measured HCO$_3^-$ + 8 (±2).

As a simple rule of thumb for chronic metabolic acidosis, the expected PaCO$_2$ approximates the last two digits of the pH value (e.g., the expected PaCO$_2$ for a pH of 7.25 is 25). Although respiratory compensation is relatively prompt (fully developed within 24 to 48 hours), it is rarely complete. If the PaCO$_2$ is above that expected for a given HCO$_3^-$, either the time for compensation has been too short or respiratory acidosis is present. If the PaCO$_2$ is less than expected, concomitant respiratory alkalosis is present. Buffering of H$^+$ by intracellular protein and fixed buffers in bone (calcium salts) represents a third major mechanism for blunting the decrease in pH. Finally, the kidneys may enhance H$^+$ excretion, but this function requires the active excretion of H$^+$ in combination with phosphate (titratable acidity) and ammonium. Such losses of H$^+$ are limited approximately to 50 to 100 mEq/day, a rate that approximates the normal pace of mineral acid production. In general, 10 to 40 mEq of H$^+$ is excreted each day as titratable acidity and 30 to 60 mEq as ammonium.

These compensatory processes are essential for maintenance of acid-base balance because the rate of excretion of free H$^+$ ions is extremely low. The kidneys respond to an increased H$^+$ load by augmenting production and subsequent excretion of NH$_4^+$. The net effect is that NH$_4^+$ excretion can exceed 250 mEq/day with severe acidemia. By contrast, there generally is only a limited ability to enhance titratable acidity because phosphate excretion remains relatively constant. One exception occurs in ketoacidosis, where excreted ketone anions can act as urinary buffers, increasing titratable acid excretion by up to 50 mEq/day.

**Treatment**
If pH disturbances are severe, therapeutic measures may be necessary to alter the PCO$_2$ or bicarbonate content directly. However, the treatment of acid-base disorders usually should be directed at the underlying cause. Mistakenly, the lack of definitive evidence proving efficacy of bicarbonate therapy in some forms of metabolic acidosis has been interpreted to imply that base therapy is futile in all situations. Potential indications for direct treatment of metabolic acidosis are (1) pH less than 7.10, (2) overt physiologic compromise attributable to acidosis, and (3) excessive work of breathing required to maintain an acceptable pH (>7.20). Exogenous HCO$_3^-$ may be needed to rebuild a “buffer base” depleted by chronic respiratory alkalosis, GI or renal losses of HCO$_3^-$, and resolved metabolic acidosis.

If bicarbonate therapy is used, calculation of the HCO$_3^-$ dose assumes a distribution into half of total body water. Total body water (in L) is approximately 0.6 times the lean body weight (in kg). The following expression

\[
\text{HCO}_3^- \text{ deficit} = (0.5 \times \text{total body water}) \times (24 - [\text{HCO}_3^-])
\]

approximates the HCO$_3^-$ deficit in mEq. Larger bicarbonate doses may be required to repair profound reductions in serum bicarbonate levels, as the apparent volume of distribution for bicarbonate then increases. Because NaHCO$_3$ has potentially adverse effects and because the effectiveness of a given dose is not entirely predictable, it is customary to replace one half the calculated HCO$_3^-$ deficit over several hours while following the pH response closely. NaHCO$_3$ partially equilibrates in total body water within 15 minutes of administration; however, cellular equilibration requires approximately 2 hours to complete.

NaHCO$_3$ administration presents several potential problems. In large doses, hypertonic hypernatremia and fluid overload may occur (an ampule of NaHCO$_3$ contains nearly as much Na$^+$ as 0.5 L of normal saline). Bolus injection of NaHCO$_3$ may elicit a biphasic ventilatory response. Immediately after administration, peripheral pH rises and the drive to breathe falls. However, soon thereafter, rising CO$_2$ (because of both metabolic load and buffered H$^+$ ion) diffuses across the blood-brain barrier to reduce intracerebral pH and stimulate breathing (“paradoxical central nervous system [CNS] acidosis”). Rapid bolus injection of NaHCO$_3$ is potentially dangerous—it may cause a rapid leftward shift of the oxyhemoglobin dissociation curve, alter cerebral hemodynamics, or induce life-threatening hypokalemia. A pH greater than 7.10 usually is sufficient to maintain near-normal vascular tone and myocardial contractility and can almost always be obtained using small doses of NaHCO$_3$. Furthermore, some types of acidosis (e.g., proximal RTA) are very difficult to correct with exogenous bicarbonate. In organic acidosis (DKA or lactic acidosis), NaHCO$_3$ therapy eventually may lead to an alkalosis as the organic acids (ketones, lactate) are recycled to HCO$_3^-$ by the liver. There is no loss of potential bicarbonate in these disorders; therefore, bicarbonate therapy is rarely necessary.

Dichloroacetate (DCA) is a compound that stimulates pyruvate dehydrogenase activity, thereby minimizing lactate production by allowing pyruvate to be oxidized to CO$_2$ and H$_2$O. Although there is evidence of benefit in experimental models of lactic acidosis, a controlled trial in humans showed that DCA produced a minor increase in the plasma bicarbonate concentration and arterial pH, but no improvement in systemic hemodynamics or mortality. Tromethamine (THAM) is an inert amino alcohol that buffers acids and CO$_2$ by virtue of its amine moiety. THAM supplements the buffering capacity of blood without generating carbon
dioxide but is less effective in patients with renal failure. Published clinical experience with THAM is limited, but the drug has been used in treating severe acidemia caused by sepsis, hypercapnia, DKA, RTA, and drug intoxication.

Metabolic Alkalosis
Metabolic alkalosis, a pH higher than 7.45 with a normal or elevated PaCO₂, usually is generated and maintained by two distinct pathophysiologic mechanisms. Metabolic alkalosis always occurs because of the gain of \( \text{HCO}_3^- \), loss of H⁺ ions, or loss of body fluids that are relatively rich in chloride. In the first situation, exogenous base may accumulate when excess bicarbonate, citrate, lactate, or acetate is administered. The second mechanism for establishing metabolic alkalosis occurs when H⁺ is lost. Loss most commonly occurs in gastric juice from nasogastric (NG) suctioning or vomiting, but this occurs less commonly with the widespread use of H₂ blockers and proton pump inhibitors. Rarely, H⁺ excretion may result from a renal disorder in which losses may be mediated by excess mineralocorticoids, increased distal tubule Na⁺ delivery, or excessive filtration of nonreabsorbable anions (e.g., calcium, penicillin). Interestingly, renal mechanisms almost never generate metabolic alkalosis but are almost always responsible for its perpetuation. The normal kidney rapidly excretes alkaline urine in response to a \( \text{HCO}_3^- \) load, provided that serum Cl⁻, K⁺, and Mg³⁺ are normal and perfusion is adequate. However, hypokalemia, hypomagnesemia, and hypochloremia all inhibit the excretion of excess \( \text{HCO}_3^- \).

Diagnostic Criteria
Metabolic alkalosis is characterized by an elevated pH, elevated \( \text{HCO}_3^- \), and often a compensatory increase in PaCO₂ if the disorder is chronic. The anion gap may increase because of the increased “charge equivalency” of albumin and stimulation of organic anion synthesis.

Signs and Symptoms
Patients with metabolic alkalosis may be asymptomatic or complain of symptoms related either to volume depletion (weakness, muscle cramps, postural dizziness) or to hypokalemia (polyuria, polydipsia, muscle weakness). Complaints directly related to alkalemia, however, are uncommon. Metabolic alkalosis impairs neural transmission and muscular contraction, especially when accompanied by hypokalemia and hypophosphatemia—two commonly coexisting abnormalities. Indeed, metabolic alkalosis mimics hypocalcemia in its symptomatology. Changes in mental status and thirst occur commonly because of volume depletion.

Precipitants of Metabolic Alkalosis
NG suctioning or vomiting can deplete circulatory volume as well as H⁺, Mg³⁺, and Cl⁻ concentrations. In replacing these H⁺ losses, \( \text{HCO}_3^- \) is generated and retained. Volume depletion causes hyperaldosteronism (retention, K⁺ loss). Aldosterone also promotes maximal Na⁺ reabsorption, leading to high rates of tubular Na⁺ for H⁺ exchange, which further worsens the alkalosis.

Relief of long-standing respiratory acidosis (e.g., with institution of mechanical ventilation) results in a rapidly evolving metabolic alkalosis because of the \( \text{HCO}_3^- \) previously retained in compensation. For unknown reasons,
chronic respiratory acidosis promotes urinary Cl⁻ wasting, which further helps to perpetuate alkalosis. Mineralocorticoid excess (primary or secondary) is commonly accompanied by K⁺ loss and impaired renal tubular \( \text{HCO}_3^- \) excretion. When loop diuretics are given to volume-depleted patients, increased amounts of Na⁺ are presented to the distal renal tubule and the resulting intensified exchange of Na⁺ for H⁺ perpetuates metabolic alkalosis. If Na⁺ is administered along with a nonresorbable anion (e.g., penicillin) to volume-depleted patients, the Na⁺ will be reabsorbed in the renal tubule, and H⁺ will be secreted to maintain electroneutrality.

The weak aldosterone-like properties of glucocorticoids may cause metabolic alkalosis in Cushing syndrome or with exogenous administration of corticosteroids. Excess \( \text{HCO}_3^- \) retention may occur after therapeutic administration, but if circulating volume and K⁺ are normal, the kidney has a remarkable ability to excrete excess \( \text{HCO}_3^- \). Iatrogenic metabolic alkalosis often complicates therapy of acidosis because of DKA, or lactate because \( \text{HCO}_3^- \) is regenerated in the recovery period.

The volume contraction of diuretic use accounts for perhaps the most commonly encountered cause of metabolic alkalosis. Contraction alkalosis is a state in which losses of intravascular volume, K⁺, and Cl⁻ act in conjunction with hyperaldosteronism to deplete ECF, whereas \( \text{HCO}_3^- \) remains nearly constant. The reactive increase of aldosterone favors reabsorption of Na⁺ and excretion of urinary H⁺. Although this problem is most commonly seen with loop or thiazide-type diuretics, it can also occur with vomiting (high gastric loss of Cl⁻).

**Maintenance of Alkalosis**

Metabolic alkalosis can be maintained by the same four mechanisms responsible for its development: Cl⁻ deficiency, mineralocorticoid excess, and depletion of circulating volume or K⁺. However, in a given patient, metabolic alkalosis often is maintained by a different mechanism from the one that established it. For example, NG removal of Cl⁻ and H⁺ may generate a metabolic alkalosis, but it is associated with depletion of intravascular volume and Cl⁻ that maintain it, even after NG suctioning is discontinued. Cl⁻ and volume must be administered for reversal. Given a choice, the body chooses to maintain adequate circulating volume status at the expense of Cl⁻ and pH homeostasis.

**Compensation for Metabolic Alkalosis**

In metabolic alkalosis, the PaCO₂ normally rises approximately 0.6 mm Hg/mmol increase in \( \text{HCO}_3^- \). (Lower PaCO₂ values indicate a superimposed respiratory alkalosis.) When breathing room air, it is rare to see a compensatory increase in PaCO₂ that exceeds 60 mm Hg, at least in part because at this level of hypercarbia, the PaO₂ falls to approximately 60 mm Hg and hypoxemia begins to drive respiration.

**Diagnosis**

As already indicated, the clinical history, the medication profile, serum chemistry, and intravascular volume status are keys to the differential diagnosis. The laboratory evaluation should be directed at differentiating chloride-responsive from chloride-resistant alkalosis (see following). A chloride-responsive alkalosis usually can be identified by measuring urine electrolytes. Such measurements are useful, provided that they are not obtained within 24 hours of diuretic administration, because most diuretics result in Cl⁻ and K⁺ losses. Urinary Cl⁻ concentrations lower than 20 mEq/L characterize a chloride-responsive condition, suggesting volume depletion or posthypercapnic alkalosis as potential mechanism. If the urine Cl⁻ concentration
exceeds 20 mEq/L, mineralocorticoid excess, diuretic use, and severe hypokalemia or hypomagnesemia are common causes. Marked disparity between urinary Cl\(^{-}\) and Na\(^{+}\) concentrations strongly suggests mineralocorticoid excess.

Table 12-4. Classification of Metabolic Alkalosis Based on Chloride Responsiveness

<table>
<thead>
<tr>
<th>Chloride Responsive</th>
<th>Chloride Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume depletion</td>
<td>Hyperaldosteronism</td>
</tr>
<tr>
<td>Vomiting/diarrhea</td>
<td>Exogenous steroids</td>
</tr>
<tr>
<td>Nasogastric suction</td>
<td>Cushing syndrome</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Alkali ingestion</td>
</tr>
<tr>
<td>Post-hypercapnia</td>
<td></td>
</tr>
<tr>
<td>Chronic medications (e.g., penicillin)</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment of Metabolic Alkalosis**

Metabolic alkalosis often is considered in two general categories—“salt” (NaCl) responsive or salt unresponsive (Table 12-4). NaCl frequently reverses volume contraction and secondary hyperaldosteronism. The “chloride dose” required to correct a chloride-responsive alkalosis can be approximated as the desired change in chloride concentration times 25% of body weight in kilogram. NaCl also provides Cl\(^{-}\) ions for reabsorption, with Na\(^{+}\) obviating the need for H\(^{+}\) secretion. (The effectiveness of NaCl replacement may be determined by measuring urinary pH—if Na\(^{+}\) replacement is sufficient, urinary pH will rise above 7.0.) Chloride, the only absorbable anion, is the critical component in NaCl administration. For example, administration of other sodium salts (e.g., sodium sulfate) will not improve metabolic alkalosis even though Na\(^{+}\) is provided and the volume is corrected. Because K\(^{+}\) depletion contributes to maintenance of metabolic alkalosis by preventing adequate HCO\(_3\)\(^{-}\) excretion, potassium chloride replacement is the preferred therapy, but quantities of potassium that can be safely given limit the rate and volume of administration.

Patients with the edematous states associated with heart failure, cirrhosis, or nephrotic syndrome often develop metabolic alkalosis following diuretic therapy, but the administration of saline is not indicated because it will increase the degree of edema. Preferred corrective therapy consists of withholding diuretics if possible, using acetazolamide, HCl, or dialysis. Acetazolamide is a carbonic anhydrase inhibitor that increases the renal excretion of sodium bicarbonate. The dose is 125 to 500 mg orally or intravenously, given with a maximum total of 1,000 mg daily.

Chloride-resistant alkaloses (adrenal disorders, corticosteroid administration, excess alkali ingestion or administration) usually occur due to mineralocorticoid excess. Therefore, in most such disorders, hypokalemia (sometimes severe) is a predictable feature. Therapy of mineralocorticoid excess may be directed at removal of the hormonal source (tumor control, withdrawal of steroids) or blockade of mineralocorticoid effect (spironolactone). K\(^{+}\)-sparing diuretics or the combination of Na\(^{+}\) restriction and K\(^{+}\) supplementation also is effective. Caution is mandated in patients who are oliguric. Rarely, metabolic alkalosis is sufficiently protracted or severe to warrant the administration of intravenous HCl. This therapy should be reserved for patients with normal...
volume status and potassium concentrations and refractory, severe, symptomatic alkalosis. HCl may be infused as a 0.1- to 0.2-M solution, but must be given directly into a central venous catheter at a rate not exceeding 0.2 mEq/kg/h. In a similar manner as calculating bicarbonate deficit, the appropriate HCl dose may be approximated from the product of the desired change in $\text{HCO}_3^-$, assuming distribution in 50% of the total lean body water. Ammonium chloride may be used instead of HCl but should not be administered to patients with renal or hepatic failure.

**Respiratory Acidosis**

Although CO$_2$ is not an acid, it combines with H$_2$O as it is added to the bloodstream, resulting in the formation of H$_2$CO$_3$. The ensuing elevation in the H$^+$ concentration is then minimized because most of the excess H$^+$ ions combine with extracellular buffers, including hemoglobin (Hgb) in red cells.

$$\text{H}_2\text{CO}_3 + \text{Hgb}^- \leftrightarrow \text{HHgb} + \text{HCO}_3^-$$

The $\text{HCO}_3^-$ generated by this reaction leaves the erythrocyte and enters the ECF in exchange for extracellular Cl$^-$. The net effect is that metabolic CO$_2$ is primarily carried in the bloodstream as $\text{HCO}_3^-$ with little change in the extracellular pH. These processes are reversed in the alveoli. As HHgb is oxygenated, H$^+$ is released. These H$^+$ ions combine with $\text{HCO}_3^-$ to form H$_2$CO$_3$ and then CO$_2$, which is excreted. The respiratory acidosis can be acute or chronic (Table 12-5).

**Acute Respiratory Acidosis**

From an acid-base perspective, the body is not well adapted to handle an acute elevation in CO$_2$ concentration. Little extracellular buffering occurs, because $\text{HCO}_3^-$ cannot buffer H$_2$CO$_3$ and the renal response takes time to develop. Consequently, the cellular buffers, particularly hemoglobin and proteins, constitute the primary modulators of acidosis related to acute hypercapnia.

<table>
<thead>
<tr>
<th>Table 12-5. Etiology of Acute and Chronic Respiratory Acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INHIBITION OF THE MEDULLARY RESPIRATORY CENTER</strong></td>
</tr>
<tr>
<td>A. Acute</td>
</tr>
<tr>
<td>1. Drugs: opiates, anesthetics, sedatives</td>
</tr>
<tr>
<td>2. Oxygen in chronic hypercapnia</td>
</tr>
<tr>
<td>3. Cardiac arrest</td>
</tr>
<tr>
<td>4. Central sleep apnea</td>
</tr>
<tr>
<td>B. Chronic</td>
</tr>
<tr>
<td>1. Extreme obesity (pickwickian syndrome)</td>
</tr>
<tr>
<td>2. Central nervous system disease (rare)</td>
</tr>
<tr>
<td>3. Metabolic alkalosis</td>
</tr>
<tr>
<td><strong>DISORDERS OF THE RESPIRATORY MUSCLES AND CHEST WALL</strong></td>
</tr>
<tr>
<td>A. Acute</td>
</tr>
</tbody>
</table>
1. Muscle weakness: myasthenia gravis, periodic paralysis, Guillain-Barré syndrome, severe hypokalemia, or hypophosphatemia

B. Chronic
1. Muscle weakness: spinal cord injury, poliomyelitis, amyotrophic lateral sclerosis, multiple sclerosis, and myxedema
2. Kyphoscoliosis
3. Extreme obesity

**UPPER AIRWAY OBSTRUCTION**
A. Acute
1. Aspiration
2. Obstructive sleep apnea
3. Laryngospasm

**DISORDERS AFFECTING GAS EXCHANGE ACROSS THE PULMONARY CAPILLARY**
A. Acute
1. Exacerbation of underlying lung disease
2. Acute respiratory distress syndrome
3. Acute cardiogenic pulmonary edema
4. Severe asthma or pneumonia
5. Pneumothorax/Pulmonary hemorrhage
B. Chronic
1. COPD: bronchitis, emphysema
2. Extreme obesity

**MECHANICAL VENTILATION**
Permissive hypercapnia
Reversal of hyperventilation

\[ H_2CO_3 + Buf \rightleftharpoons HBuf + HCO_3^- \]

As a result of these buffering reactions, there is an increase in the plasma \( HCO_3^- \) concentration, averaging 1 mEq/L for every 10 mm Hg rise in the PCO₂.

The common causes of acute respiratory acidosis include acute exacerbation of such underlying lung diseases as severe asthma or pneumonia, pulmonary edema, and suppression of the respiratory center following a cardiac arrest, a drug overdose, or the administration of oxygen to a patient with chronic hypercapnia.

**Chronic Respiratory Acidosis**
Persistent elevation in the PaCO₂ stimulates renal H⁺ excretion, resulting in the addition of \( HCO_3^- \) to the ECF. The net effect is that, after 3 to 5 days, a new steady state is attained in which there is roughly a 3.5 mEq/L increase in the plasma \( HCO_3^- \) concentration for every 10 mm Hg increment in the PaCO₂. The efficiency of the renal compensation has allowed some patients to tolerate PaCO₂ values as an ongoing bases as high as 90 to 110 mm Hg, without a fall in the arterial pH to less than 7.25 and without symptoms as long as adequate
oxygenation is maintained. Chronic respiratory acidosis is a relatively common clinical disturbance that is most often because of chronic obstructive lung disease (bronchitis and emphysema) in smokers.

**Symptoms**

Severe acute respiratory acidosis can produce a variety of neurologic abnormalities. The initial symptoms include headache, blurred vision, restlessness, and anxiety, which can progress to tremors, asterixis, delirium, and somnolence (called CO₂ narcosis). The cerebrospinal fluid pressure is often elevated, and papilledema may be seen. Arrhythmias and peripheral vasodilatation can produce hypotension if the systemic pH falls below 7.10. Chronic respiratory acidosis is also associated with cor pulmonale and peripheral edema. The cardiac output and glomerular filtration rate are usually normal in this disorder.

**Diagnosis**

The presence of an acid pH and hypercapnia associated with a ventilatory disorder is diagnostic of respiratory acidosis. However, identifying the underlying acid-base disorder is more complicated than in metabolic acidosis or alkalosis, and the clinical context is essential. Compensated chronic respiratory acidosis is recognized by clinical history of pulmonary pathology, elevated CO₂, and a blood pH that is maintained at a nearly normal level.

Uncompensated chronic respiratory acidosis is recognized by the clinical history of pulmonary pathology, elevated CO₂, and acidotic blood pH.

**Treatment of Respiratory Acidosis**

Patients with acute respiratory acidosis are at risk of both hypercapnia and hypoxemia. Although the PaO₂ can usually be raised by the administration of supplemental oxygen, reversal of the hypercapnia requires an increase in effective alveolar ventilation. This can be achieved by control of the underlying disease (as with bronchodilators and corticosteroids in asthma) or by mechanical ventilation delivered via either a tight-fitting mask or an endotracheal tube. The role of an alkalinizing agent in this setting is controversial and usually considered primarily when the hemodynamic status of the patient is compromised. THAM has been used in this setting, and the reported results have been satisfactory. Under some conditions, bicarbonate can increase intracellular acidosis.

The primary goals of therapy in patients with chronic respiratory acidosis are to maintain adequate oxygenation and, if possible, to improve effective alveolar ventilation per se. Because of the effectiveness of the renal compensation, it is usually not necessary to treat pH, even in patients with severe hypercapnia. The appropriate treatment varies with the underlying disease.

**Respiratory Alkalosis**

**Inciting Mechanisms**

Respiratory alkalosis—primary or compensatory—is defined by hypocapnia, a finding that implies alveolar hyperventilation. Central neurologic disorders, agitation, pain, inappropriate mechanical ventilation, hypoxemia, and restrictive diseases that reduce respiratory system compliance all may produce primary respiratory alkalosis.

**Symptoms**
Acute respiratory alkalosis usually is manifest by tachypnea; however, when chronic, this disorder may be associated with large tidal volume breaths at near-normal respiratory rates. The symptoms of acute respiratory alkalosis, “the hyperventilation syndrome,” vary only in intensity from those of any alkalosis—most notably impaired neuromuscular function (e.g., paresthesias, tetany, tremor). A constellation of symptoms has been described with respiratory alkalosis, including chest pain, circumoral paresthesias, carpopedal spasm, anxiety, and light-headedness.

**Compensatory Mechanisms**

Protracted respiratory alkalosis induces renal $\text{HCO}_3^-$ wasting to offset hypocapnia. When the stimulus for hyperventilation is removed, hyperpnea tends to continue, driven by CNS acidosis until intracerebral $\text{HCO}_3^-$ and pH are fully corrected.

**MIXED ACID-BASE DISORDERS**

Renal and respiratory compensation returns the pH toward, but rarely to, normal. Thus, a normal pH in the presence of changes in the $\text{PaCO}_2$ and plasma $\text{HCO}_3^-$ concentration immediately suggests a mixed disorder. Complex (mixed) acid-base disorders occur most frequently when lung and renal diseases coexist, when compensatory mechanisms are rendered inoperative, or when mechanical ventilation is used. The presence of a complex or mixed acid-base disorder is discovered by applying the rules of expected compensation given earlier and in Chapter 5.

One particular condition, the “triple acid-base disorder,” deserves special mention. It should be recognized that the term triple acid-base disorder has no unique interpretation. It could refer to three simultaneous metabolic acidoses or alkaloses or any combination of metabolic processes. However, because respiratory acidosis and respiratory alkalosis cannot coexist, the so-called triple acid-base disorder is the result of two metabolic derangements and a single ventilation abnormality.

**SUGGESTED READINGS**


Key Points


2. The diagnosis of the etiology of hyponatremia relies on serum osmolality and an accurate assessment of fluid balance. In many cases, the etiology can be determined by history and physical examination.

3. Acutely occurring severe hyponatremia (serum Na⁺ < 120 mEq/L) defines an urgent clinical situation in which levels of the ion should be raised to 120 mEq/L or above. Correction should be approximately 1 to 2 mEq/L/h in patients with severe neurologic symptoms (stupor, coma, seizures, etc.) and then slower once the life-threatening symptoms are reversed. Water restriction, isotonic saline and hypertonic saline are appropriate for hypervolemic, hypovolemic and isovolemic hyponatremias, respectively.

4. Hypermantremia usually is the result of restricted access to free water or absence of the sensation of thirst. Rarely, central diabetes insipidus, treated with antidiuretic hormone, is the etiology. Diabetes insipidus can be clinically recognized by large volumes of dilute urine in a patient with hyperosmolar serum.

5. Because little of the body's potassium is in the extracellular compartment, significant hypokalemia signals total body depletion of potassium, usually by more than 200 mEq. Because of the importance of potassium in maintaining normal neural, cardiac rhythm and muscular functioning, prompt correction of the deficit is prudent. When possible, oral replacement avoids the rapid potassium level changes associated with IV dosing. When IV replacement is used, dosing should probably be limited to 20 to 40 mEq/h.

6. Significant hyperkalemia usually is the result of renal insufficiency. Hyperkalemia sufficient to induce electrocardiographic changes should be treated aggressively with volume expanders, loop diuretics, insulin, glucose, bicarbonate (in the presence of acidosis), and intravenous calcium. Potassium removal using dialysis or binding resins is also indicated for specific situations.

7. Both calcium and magnesium depend on their ionized forms for biologic action; therefore, total serum concentrations do not accurately reflect bioactivity. Total calcium and magnesium levels, and their ionized forms, should be measured when unexplained neuromuscular disorders or cardiac arrhythmias occur in the ICU.

Disorders of Sodium and Osmolality

Despite great variability in sodium (Na⁺) and water intake, circulating intravascular volume, serum Na⁺ concentration, and osmolality normally remain quite stable. Total body water is controlled by two main mechanisms: plasma osmolality (pituitary osmolar receptors) and carotid body regulation via nonosmolal receptors. As a consequence of dehydration and/or hypovolemia, increases in serum osmolality may occur that trigger increased thirst (hypothalamic stimulation), and secretion of antidiuretic hormone (ADH) from the posterior pituitary. Although they often coexist, it is essential to recognize that dehydration (loss of water) is different from hypovolemia (inadequate circulating volume). ADH secretion increases dramatically as osmolality rises above 285 mOsm/L or extracellular volume declines by 10% to 15%. ADH then acts on the medullary collecting duct of the kidney to stimulate water reabsorption. The renin-angiotensin-aldosterone system restores the circulating volume in response to its contraction. The combined effects of ADH and the renin system balance the retention...
of Na\(^+\) and water. When plasma osmolality declines, ADH release is inhibited, and excess water is lost in an attempt to return osmolality toward normal.

Hence, usually the serum Na\(^+\) concentration has little to do with the amount of Na\(^+\) in the body, but much to do with the amount of water.

**Hyponatremia**

Disorders of fluid and Na\(^+\) balance occur daily in the intensive care unit (ICU) because patients have multiple organ system failure, are usually denied self-regulation of water balance, and are administered medications that disturb fluid and electrolyte status. Hyponatremia, defined as a serum Na\(^+\) concentration less than 135 mEq/L, is one of the most common electrolyte disorders and implies excess body water. The manifestations of hyponatremia range from the subtle to the neurologically profound but generally are proportional to the magnitude of the hyponatremia and the speed with which it develops. Symptoms span the spectrum from muscle cramps, nausea, vomiting, and anorexia to confusion, lethargy, coma, and seizures.

In combination with a thorough history, medication review, and physical examination, the serum osmolality, glucose, creatinine, and albumin provide essential data for determining the etiology of hyponatremia. Because Na\(^+\) is the predominant osmotically active extracellular cation, serum osmolality is normally determined largely by the relative proportions of water and Na\(^+\). Measurements of serum osmolality help to separate hyponatremic disorders into three distinct categories, summarized in **Table 13-1**. Apart from disturbances in sodium/water balance, marked elevations of glucose or presence of exogenous substances (alcohols and complex carbohydrates) can elevate serum osmolality. Conversely, reductions in osmolality virtually always are reflected in the Na\(^+\) concentration, as illustrated by the equation commonly used to calculate serum osmolality:

<table>
<thead>
<tr>
<th>Table 13-1. Hyponatremia: Diagnostic Categories and Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertonic Hyponatremia</strong></td>
</tr>
<tr>
<td>Hypovolemic</td>
</tr>
<tr>
<td>Osmotic agents</td>
</tr>
<tr>
<td>Glucose</td>
</tr>
<tr>
<td>Mannitol</td>
</tr>
<tr>
<td>Starch</td>
</tr>
<tr>
<td>Diuretics (thiazide, loop, and osmotic)</td>
</tr>
<tr>
<td>Third-space loss</td>
</tr>
</tbody>
</table>


Categories of Hyponatremia

Hypertonic Hyponatremia

Hypertonic hyponatremia results from infusion or spontaneous generation of (nonsodium) osmotically active substances. Hyperglycemia and therapeutic administrations of hypertonic glucose, mannitol, or glycine can cause hypertonicity while depressing Na\(^+\) levels. (Although urea also increases osmolality, it fails to affect serum Na\(^+\) concentration because it freely traverses cell membranes, dissipating any potential osmotic gradient.) Extracellular hypertonicity draws water from cells in an attempt to reduce the osmotic gradient. This effect partially corrects serum hyperosmolality but also lowers the Na\(^+\) concentration while causing cellular dehydration. The cause of hypertonic hyponatremia usually can be diagnosed by measuring serum glucose and reviewing a list of the patient's drugs. When hyperglycemia is the etiology, Na\(^+\) levels decline approximately 1.6 mEq/L per 100 mg/dL rise in serum glucose. Thus, hyperglycemia has a negligible effect on Na\(^+\) levels at concentrations less than 200 to 300 mg/dL.

Hypotonic Hyponatremias

Hypotonic hyponatremia, the most common form of hyponatremia, can be subclassified into three categories based upon the estimation of the patient's volume status. Hypotonic hyponatremia almost never develops unless the patient has unrestricted access to water or receives a hypotonic fluid.

HYPOVOLEMIC HYPOTONIC HYponATREMIA

Hypovolemic hyponatremia with low serum osmolality results from replacing losses of salt-containing plasma with hypotonic fluid. Volume depletion is a potent stimulus for ADH release. Intake of hypotonic fluid, when combined with the decreased free water clearance that results from ADH release, causes hyponatremia. Physical examination reveals signs of volume depletion. Thirst and postural hypotension are more objective and reliable signs than are skin turgor, sunken orbits, and dryness of mucous membranes.

Hypovolemic hypotonic hyponatremia may result from renal or nonrenal causes. Bleeding, diarrhea, vomiting, and profuse sweating are common nonrenal mechanisms of circulating volume loss and are usually apparent clinically. Third-space losses (e.g., pancreatitis or gut sequestration) may be less obvious. Renal causes of volume depletion and hyponatremia include diuretic use (particularly thiazide diuretics); osmotic diuresis from ketones, glucose, or mannitol and the less common conditions of mineralocorticoid deficiency; and salt-wasting nephropathy.

For patients with well-functioning kidneys and normal levels of mineralocorticoid hormones, small volumes of hypertonic urine with a very low Na\(^+\) concentration reflect intense conservation of Na\(^+\) and water. If the cause of the syndrome is not clear from the history and physical examination, measuring urine Na\(^+\) and osmolality and serum cortisol and aldosterone may be diagnostically helpful. If urine Na\(^+\) concentration is high and urine osmolality normal, renal salt wasting is the probable etiology. With mineralocorticoid insufficiency, the urine Na\(^+\)
concentration is high and the urine osmolality is elevated. Because hypovolemia reduces renal perfusion, thereby slowing tubular flow, urea may “back-diffuse” into the bloodstream, so the BUN/creatinine ratio rises. Similarly, uric acid levels tend to rise.

Cerebral salt-wasting syndrome is an uncommon problem described in patients with intracranial pathology, particularly subarachnoid hemorrhage. High urine Na\(^+\) concentration is thought to arise from the release of a brain natriuretic peptide-like substance. The urine has a high Na\(^+\) concentration and a low uric acid level. In cerebral salt wasting, urinary uric acid concentration remains low despite reversal of hyponatremia.

**ISOVOLEMIC HYPOTONIC HYPONATREMIA**

Isovolemic hypotonic hyponatremia is a bit of a misnomer, as a clinically inapparent but slight excess of total body fluid (3 to 4 L) frequently exists. Inappropriate secretion of antidiuretic hormone (SIADH) and water intoxication are the two most frequent causes. Most cases of water intoxication occur in patients with impaired ability to clear free water or ADH excess. For example, water intoxication occurs with increased frequency when renal disease (decreased clearance) complicates schizophrenia (increased ADH and increased water intake). Another common clinical setting is the postoperative patient given hypotonic IV fluid or tap water enemas (increased ADH and increased water intake). Diuretics can also cause isovolemic hyponatremia in a patient with unlimited water access, as natriuresis impairs free water clearance and sensitizes to ADH. Because hypothyroidism and hypocortisolism are relatively common causes of isovolemic hypotonic hyponatremia, thyroid and adrenal function must be tested. Ecstasy (MDMA) use should be suspected in otherwise healthy young patients presenting with isovolemic hypotonic hyponatremia. Ecstasy tends to cause water loss by increasing body temperature and activity, and some users obsessively drink water to prevent dehydration.

Inappropriate ADH syndrome (SIADH) is a diagnosis of exclusion, which requires near-normal volume status, normal cardiac and renal function, and a normal hormonal environment (exclusive of ADH). Because the requisite conditions are often not met, SIADH is overdiagnosed. SIADH-induced volume expansion increases cardiac output and glomerular filtration rate (GFR), eventually depleting the stores of total body Na\(^+\). (Because a constant fraction of filtered Na\(^+\) is reabsorbed, there is obligatory renal loss of Na\(^+\).) Serum values of Na\(^+\), creatinine, and uric acid are all subnormal because of the expanded circulating volume and increased GFR. SIADH is most frequently associated with malignant tumors, particularly of the lung; however, central nervous system (CNS) or pulmonary infections, drugs (Table 13-2), and trauma also may be causative. SIADH is characterized by inappropriately concentrated urine; osmolality of the urine typically exceeds that of plasma. Urine Na\(^+\) concentrations are more than 20 mEq/L, and the urine cannot be diluted appropriately in response to water loading. (When water-challenged, patients with most other types of hyponatremia completely suppress ADH release to excrete maximally diluted urine of less than 100 mOsm/L.)

<table>
<thead>
<tr>
<th>Neurologic Disorders</th>
<th>Cancers</th>
<th>Pulmonary Disorders</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>Lung carcinoma</td>
<td>Tuberculosis</td>
<td>Narcotics</td>
</tr>
<tr>
<td>Stroke</td>
<td>Pancreatic carcinoma</td>
<td>Pneumonia</td>
<td>Chlorpropamide</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td>Tolbutamide</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Cyclophosphamide</td>
</tr>
</tbody>
</table>

*Table 13-2. Causes of Inappropriate ADH Syndrome*
The treatment of isovolemic hypotonic hyponatremia depends on its cause. If tumor related, appropriate antineoplastic therapy can be helpful. Replacement of thyroid hormone or cortisol reverses the defect in hypothyroidism or adrenal insufficiency. In SIADH, treatment prioritizes restriction of free water.

**HYPERVOLUMIC HYPOTONIC HYponATREMIA**

Edema is the hallmark of hypervolemic hypotonic hyponatremia, a syndrome in which water is retained in excess of Na\(^+\). Because approximately 60% of total body water is intracellular, a 10 L excess of total body water is often present in the supine patient before enough interstitial fluid accumulates to cause clinically notable edema (unless hypoalbuminemia or vascular permeability is increased). Despite increases in both total body water and Na\(^+\), effective intravascular volume usually is modestly decreased.

The basic problem in this condition is that the kidney cannot excrete Na\(^+\) and water at a rate sufficient to keep pace with intake. Reduced Na\(^+\) and water clearance can be the result of intrinsic renal disease or conditions that decrease effective renal perfusion (congestive heart failure, cirrhosis, malnutrition, and nephrotic syndrome). Renal causes include almost any form of acute or chronic renal failure.

If the cause is extrarenal, there is intense conservation of Na\(^+\) and water with very low urinary Na\(^+\) concentrations (<10 mEq/L), low urine volumes, and high urine osmolality. Urine electrolytes and osmolality are more variable (and less helpful) in kidney disorders. Because diuretics impair the ability to conserve Na\(^+\) and water, at least 24 hours must elapse between the last dose of diuretic and determinations of urinary electrolytes and osmolality.

**Isotonic Hyponatremia**

Hyponatremia with normal serum osmolality occurs when large volumes of isotonic, non-salt-containing solutions (glucose, hydroxyethyl starch, mannitol, glycine, etc.) are retained in the extracellular space. This volume expansion does not cause a transcellular shift of water. One of the most common settings for the syndrome occurs following transurethral prostatectomy. Massive absorption of bladder irrigants containing 5% mannitol can cause isotonic hyponatremia. However, if the irrigant used is 1.5% glycine or 3.3% sorbitol, hypotonic hyponatremia may ensue. Such patients can develop severe symptomatic hyponatremia. Isotonic hyponatremia can also occur in severe paraproteinemia (usually protein concentrations > 12 to 15 g/dL) or hypertriglyceridemia. In these conditions, water constituting the liquid portion of blood and its corresponding Na\(^+\) is displaced by protein or fat, leading to an artifact in the laboratory measurement.

**Treatment of Hyponatremia**

Regardless of etiology, hyponatremia primarily affects the CNS. As the Na\(^+\) concentration acutely drops below 125 mEq/L, changes in cognition and motor function occur commonly. Confusion and seizures often occur at serum values less than 120 mEq/L, particularly if the decline occurs abruptly. The severity of the complications increases rapidly with further declines of Na\(^+\) concentration; many patients with severe hyponatremia (Na\(^+\) < 105 mEq/L) die.

While clearly there are risks from hyponatremia, there are also risks of treating it. Even though there are no
definitive studies of the topic, it is generally agreed that the speed of correction should be adjusted for the
chronicity of the problem. Unfortunately, the clinician often does not know the duration of hyponatremia.

Practically speaking, most symptomatic hyponatremic patients should have the Na\(^+\) corrected to an initial level of 120 to 130 mEq/L over a 12- to 24-hour period, at an hourly rate not to exceed 1 to 2 mEq/L. Correction should not exceed 12 mEq/L/day. Slower correction (i.e., 0.5 mEq/L/h) is prudent in patients with chronic hyponatremia. Rapid correction of longstanding hyponatremia is associated with serious neurologic sequelae—central pontine myelinolysis (CPM). CPM is a CNS demyelinating syndrome characterized by weakness, dysarthria, dysphagia, coma, and risk of death. Predispositions include not only the rate of hyponatremia correction but also severity of the hyponatremia, advanced age, preexisting liver or CNS disorders, diuretic use, and alcoholism. CPM affects the pons and other areas of the CNS. Many patients survive to a high functional level despite significant early severity of neurologic deficits. Many of these patients require mechanical ventilation, with some requiring tracheostomy and gastrostomy tubes. Recovery may not be easily predictable based on the severity of presenting illness. Because even patients with tetraparesis are capable of recovery, fully supportive care should be considered for several weeks before concluding that this condition is hopeless.

The treatment of hyponatremia depends on its cause and severity. In hypervolemic hyponatremia, restrictions of salt and fluid are the mainstays of therapy. However, diuretics or dialysis may be required when renal function is impaired. In most patients with hypovolemic hyponatremia, isotonic saline should be cautiously given to restore circulating volume. (Remember that 0.9% saline is significantly “hypertonic” for severely hyponatremic patients.) In isovolemic hyponatremia, free water restriction and treatment of the underlying disorder are preferred. In less-acute cases of SIADH, hyponatremia may respond to demeclocycline (600 to 1,200 mg/day).

Most patients with severe and symptomatic hyponatremia (stupor, coma, seizures, etc.) require hypertonic saline and/or diuretics to achieve safe serum Na\(^+\) with adequate speed. Relatively small increases in serum Na\(^+\) on the order of 5% should decrease cerebral edema. One should slow the correction once life-threatening manifestations have improved, typically to approximately 0.5 mEq/L/h. One way to calculate the amount of Na\(^+\) to be given using 3% saline follows. Multiply the desired change in serum Na\(^+\) times the estimated total body water to get the number of mEq of Na\(^+\) to be administered. Divide that amount by the concentration of Na\(^+\) in the fluid to be infused (513 mEq/L for 3% saline) to obtain the total volume to be administered. Then divide the total volume by the time over which the correction is desired to yield the infusion rate.

Example: A 60-kg woman with normal preoperative electrolytes develops seizures postoperatively while receiving hypotonic fluid. The serum Na\(^+\) is 116 mEq.

Calculation to raise the serum Na\(^+\) to 120 mEq over 4 hours is as follows:

- \(\text{Na}^+ \text{ required (mEq)} = (120 - 116) \times (0.5 \times 60 \text{ kg}) = 4 \times 30 = 120 \text{ mEq}\)
- \(\text{Volume of 3% saline (mL)} = 120 \text{ mEq} / [513 \text{ mEq/L}] = 233 \text{ mL}\)
- \(\text{Infusion rate} = 233 \text{ mL/desired infusion time (4 hours)} = 58 \text{ mL/h}\)

### Hypernatremia

**Etiology and Pathophysiology**

Hypernatremia, defined as a serum Na\(^+\) level more than 145 mEq/L, occurs when more water than Na\(^+\) is lost from the body or when highly concentrated Na\(^+\) solutions are administered or ingested. Hypernatremia is relatively uncommon, both in the overall hospital population (1%) and among critical care patients (9%). Hypernatremia is rare in patients with intact ADH secretion, a sensitive thirst mechanism, and access to free
water. Hence, it is primarily a disease of patients who are unable to obtain and drink fresh water (e.g., infants, elderly, bedridden, and critically ill), particularly those simultaneously sustaining increased water losses (e.g., diuretics, sweating). Hypernatremia implies hyperosmolarity, which is the major mediator of toxicity.

Like hyponatremia, the problem can logically be thought of in three categories: high, normal, or low extracellular volume. Hypervolemic hypernatremia occurs from ingestion or infusion of hypertonic Na+-containing solutions. For example, “normal” saline (0.9% NaCl) is modestly hypertonic (Na⁺ 154 mEq/L, 308 mOsm/L) and therefore tends to raise the serum Na⁺ concentration while expanding extracellular volume. Hypernatremia is much more common when osmolarity is intentionally increased by hypertonic (3%) saline (Na⁺ 513 mEq/L, 1,026 mOsm/L) or unintentionally by multiple ampules of sodium bicarbonate (Na⁺ of 595 mEq/L and 1,190 mOsm/L). Three percent saline is now a widely used therapy for intracranial hypertension from cerebral edema. In this setting, serum hypertonicity attracts water from cerebrospinal fluid and brain cells, reducing intracranial pressure and facilitating cerebral blood flow. For this effect, serum Na⁺ is typically maintained in the 145- to 155-mEq/L range (roughly 300 to 320 mOsm/L). Hypernatremia can be an unintended consequence of NaHCO₃ if large volumes are administered to treat metabolic acidosis or cyclic antidepressant overdose. For patients with impaired Na⁺ clearance, the Na⁺-K⁺ ion exchange resin, Kayexalate, can raise serum Na⁺ by transferring significant salt loads across the bowel wall. Na⁺ accumulation from primary hyperaldosteronism or salt or seawater ingestion are rare causes of hypernatremia.

Extracellular volume is normal, at least initially, in a number of hypernatremic conditions. For example, both central and nephrogenic diabetes insipidus (DI) produce hypernatremia by preventing appropriate water reabsorption by the distal convoluted tubules and collecting ducts of the kidney. In central DI, ADH secretion is inadequate, and in nephrogenic DI, the kidney does not respond normally to the secreted ADH. Hypernatremia with near-normal extracellular volume can also result from insensible water losses associated with burns, tachypnea, hyperthermia, and syndromes associated with fever such as heatstroke, neuroleptic malignant syndrome, and malignant hyperthermia.

<table>
<thead>
<tr>
<th>Urine Osmolarity (mOsm)</th>
<th>Differential Diagnosis</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;800</td>
<td>Dehydration</td>
<td>Free water replacement</td>
</tr>
<tr>
<td></td>
<td>Hypodipsia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sodium intoxication</td>
<td></td>
</tr>
<tr>
<td>300-800</td>
<td>Osmotic diuretics</td>
<td>Free water replacement</td>
</tr>
<tr>
<td></td>
<td>Partial or mild DI</td>
<td>Trial of ADH</td>
</tr>
<tr>
<td>&lt;300</td>
<td>Central or nephrogenic DI</td>
<td>Free water replacement and ADH therapy</td>
</tr>
</tbody>
</table>
Hypernatremia may also result from conditions causing low extracellular volume such as vomiting, diarrhea, and osmotic diuretics such as glucose, mannitol, and glycerol. Tonicity of fluid lost must be less than that of serum for hypernatremia to develop.

**Diagnosis**

Common symptoms of all forms of hypernatremia are thirst, nausea, and vomiting progressing to agitation, stupor, and coma. All of these symptoms are nonspecific, and their cause many go unrecognized. History and physical examination typically identify the correct diagnosis. It is usually obvious when NaHCO₃, 3% NaCl, or osmotic diuretics have been administered. Impressive urine output of a volume-replete patient with full-blown DI (up to 1 to 2 L/h) is also almost always noted. It is important to note that the diagnosis of DI may be missed if free water losses have progressed to the point that profound intravascular volume depletion has occurred. For example, in the unstable, volume-depleted patient in the ICU, the traditional “water deprivation test” may prove harmful. A safer strategy is replacement of circulating volume and an empiric trial of ADH. When hemodynamically stable, additional endocrine testing may be performed. While hypernatremia usually does not present a diagnostic challenge, urine osmolarity is helpful if etiology is unclear (Table 13-3).

**Treatment**

Treatment of hypernatremia consists of replacement of water either enterally or intravenously as D₂W or a hypotonic NaCl solution, with frequent evaluation of electrolytes and osmolality. The speed of correction depends on the chronicity of the problem and the severity of neurologic symptoms. As a general rule, correction of serum sodium at the rate of 0.5 to 1 mEq/L each hour is an appropriate target. It is also appropriate to limit correction rates to 12 mEq/L per day or 18 mEq/L over 2 days. Like hyponatremia, very rapid correction, particularly of long-standing hypernatremia, may precipitate CPM or cerebral edema. The latter condition results from rapid swelling of neurons that have accumulated “idiogenic osmoles” in an attempt to match the tonicity of serum during hypernatremia. If endogenous ADH is deficient or ineffective, it may be replaced with desmopressin (DDAVP), an ADH analog (see Chapter 32). In the less common cases of hypernatremia resulting from Na⁺ gain, such as after the NaHCO₃ administration in cardiac arrest, the use of loop diuretics or addition to Na⁺ poor fluid may be appropriate.

Unnecessarily precise calculations of “water deficit” are often performed in hypernatremia. It is important to recognize that the use of the conventional water deficit formula—Water deficit = (0.6 × weight) × (1 - [140/serum sodium concentration])—has limitations. It may underestimate the free water need in cases of hypotonic fluid losses (e.g., vomiting) and does not take into account ongoing insensible losses. Because Na⁺ concentrations less than 155 mEq/L seldom concern clinicians, by the time the decision is made to treat hypernatremia in the average-sized adult, water deficits average 4 to 6 L. If the goal is to correct the deficit over 1 to 2 days, IV infusion of D₂W at 200 mL/h is usually effective unless the initial Na⁺ concentration is much higher or ongoing water losses are substantial.

**POTASSIUM DISORDERS**

Ninety-eight percent of the total body potassium is intracellular. As the most abundant intracellular cation,
Potassium is a strong determinant of intracellular osmolality. Muscle contractability and heart and nerve electrical conduction depend upon the ratio between intracellular and extracellular potassium, a relationship that determines cell membrane polarization.

Most intracellular potassium resides in muscle cells. Body potassium stores in a typical adult total about 3,500 mEq. A true alteration in extracellular potassium measured as a decrease or increase in the measured level of 1 mEq/L indicates a change in total body potassium of 100 to 200 mEq.

Plasma potassium concentration is maintained within narrow limits. Two cooperative systems accomplish this. The first is the equilibrium of potassium across the cell membrane. This equilibrium may be modified by insulin, catecholamines, acid-base disturbances, plasma tonicity, and other factors. The second system affecting potassium homeostasis regulates potassium elimination and intake (which averages 50 to 150 mEq daily). Kidneys are responsible for elimination of 95% of daily potassium load with the remainder exiting through the gut. Potassium is regulated and excreted in the distal nephron.

**Hypokalemia**

Because normal obligatory K\(^+\) losses are only 5 to 10 mEq/day, and because the intracellular storage pool of K\(^+\) is very large, hypokalemia is uncommon unless substantial losses or impaired intake occurs for a substantial period of time. As a corollary, once hypokalemia (K\(^+\) < 3.5 mEq/L) becomes manifest, the average deficit is large—250 to 300 mEq (5% to 10% of the total body stores). Similarly, because repleting intracellular K\(^+\) requires the ions to traverse the small intravascular compartment, even modest K\(^+\) doses may induce hyperkalemia if given rapidly. Systemic pH significantly influences extracellular K\(^+\) concentrations. In patients with acidosis, hydrogen ions move into cells in exchange for K\(^+\). Therefore, hypokalemia observed during acidosis suggests an even larger total-body deficit.

**Etiology**

Hypokalemia may result from decreased intake, increased losses, or redistribution of K\(^+\). Measurement of urinary K\(^+\) and chloride (Cl\(^-\)) concentrations and pH is very helpful in determining the etiology of hypokalemia (Table 13-4). If urinary K\(^+\) levels are less than 20 mEq/L, either decreased intake or excessive GI losses are to blame. (The normally functioning kidney can reduce K\(^+\) excretion to less than 10 mEq/day, a level almost always less than intake.) Furthermore, although the K\(^+\) content of stool may reach 60 mEq/L, GI losses are rarely severe enough to produce symptomatic hypokalemia. (Exceptions include cholera-like illnesses, cathartic abuse, and villous adenomas.) Likewise, losses of K\(^+\) directly from gastric fluid are minimal. Thus, vomiting induces hypokalemia—not through direct losses but by promoting renal K\(^+\) wasting as a result of volume depletion and hypochloremic metabolic alkalosis.

<table>
<thead>
<tr>
<th>Table 13-4. Urine Electrolytes in Hypokalemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>If Urinary Potassium &gt; 20 mEq/L</td>
</tr>
<tr>
<td>Normal acid-base status</td>
</tr>
<tr>
<td>Urine Cl(^-) &lt; 10</td>
</tr>
<tr>
<td>Urine Cl(^-) &gt; 10 mEq/L</td>
</tr>
</tbody>
</table>
If the urinary K⁺ concentration is high (>20 mEq/L), measurement of arterial pH and urinary Cl⁻ helps determine the cause. High urinary K⁺ with acidosis usually is caused by renal tubular acidosis or diabetic ketoacidosis. If high urinary K⁺ losses are accompanied by alkalosis, urinary Cl⁻ becomes the key to diagnosis. A low value (<10 mEq/L) is indicative of diuretic use, vomiting, or nasogastric suction, all of which are usually clinically evident. Diuretic use constitutes the most common cause of hypokalemia. Diuretics increase distal tubular flow, promoting the exchange of Na⁺ for K⁺, induce secondary hyperaldosteronism, and encourage alkalosis. The latter results in a shift of K⁺ from the extracellular to the intracellular compartment. A high urinary K⁺ accompanied by an elevated urinary Cl⁻ concentration (>10 mEq/L) and alkalosis usually is due to mineralocorticoid excess (e.g., primary hyperaldosteronism, Cushing syndrome, cirrhosis, or intravascular volume depletion). Magnesium is a cofactor for the enzyme Na⁺-K⁺ ATPase, which may be a partial explanation for high renal K⁺ losses observed in patients with hypomagnesemia.

A number of events that facilitate K⁺ entry into cells may cause hypokalemia without loss of K⁺ from the body. For example, high insulin levels, whether exogenous or induced by continuous parenteral or enteral alimentation, increase cellular uptake. Metabolic alkalosis also drives K⁺ into cells in exchange for H⁺. In turn, hypokalemia increases renal HCO₃⁻ absorption, perpetuating the alkalosis. In addition, administration of β-adrenergic agonists facilitates transport of K⁺ from blood into cells, but plasma K⁺ rarely declines by more than 0.5 mEq/L.

### Pathophysiology

Hypokalemia increases the resting membrane potentials of neural and muscular tissues, reducing excitability. Hypokalemia impairs muscle contractility and, when severe (K⁺ < 2.5 mEq/L), may cause profound, even life-threatening muscle weakness. The severity of the muscular effects of a given K⁺ level depends on pH, calcium ion concentration, and the rapidity with which hypokalemia developed. The muscles of the lower extremities usually are the first to be affected, followed by those of the trunk and the

<table>
<thead>
<tr>
<th>Drug or electrolyte disorder likely</th>
<th>Diabetic ketoacidosis</th>
<th>Diuretics</th>
<th>Mineralocorticoid excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>Renal tubular acidosis</td>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td></td>
<td>Gastric suction</td>
<td></td>
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<tr>
<td>Aminoglycosides</td>
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<tr>
<td>Platinum compounds</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypomagnesemia</td>
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</tbody>
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<table>
<thead>
<tr>
<th>If Urinary Potassium &lt; 20 mEq/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrarenal mechanism is etiologic</td>
</tr>
<tr>
<td>Decreased dietary intake</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
</tbody>
</table>
respiratory system. Even moderate degrees of hypokalemia may impair smooth muscle function, producing ileus, or intestinal pseudoobstruction. Severe hypokalemia also impairs the vascular smooth muscle response to catecholamines and angiotensin, influencing blood pressure stability. Severe hypokalemia promotes cell membrane damage, resulting in rhabdomyolysis. Although focal neurologic findings rarely result from hypokalemia, lethargy and confusion can occur in severe K\(^+\) depletion. Virtually any arrhythmia may surface during hypokalemia, particularly in the presence of digitalis. Mild hypokalemia delays ventricular repolarization and is manifested by ST-segment depression, diminished or inverted T waves, heightened U waves, and a prolonged QU interval (Fig. 13-1). When hypokalemia is severe (K\(^+\) < 2.5 mEq/L), P wave amplitude, PR interval, and QRS duration increase.

![FIGURE 13-1. ECG manifestations of hypokalemia.](image)

**Treatment**

Total body deficits of K\(^+\) usually exceed 200 mEq in patients with hypokalemia. Hence, it should not be surprising that the common practice of administering a small KCl replacement dose (i.e., 20 to 40 mEq) almost always is inadequate for correction. However, because the intracellular space must be accessed via the small intravascular compartment, K\(^+\) therapy (especially intravenous replacement) must be cautiously undertaken and closely monitored to avoid potentially dangerous hyperkalemia. Because of the limited capacity to excrete K\(^+\), special care must be exercised when replacing K\(^+\) in patients with renal disease or diabetes and in those receiving drugs that block renin, angiotensin, or prostaglandin activity. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), potassium-sparing diuretics (e.g., spironolactone), and nonsteroidal anti-inflammatory drugs (NSAIDs) are all examples of such medications. Almost every condition that causes hypokalemia also causes magnesium wasting. Hypomagnesemia aggravates the physiologic effects of hypokalemia and renders deficit correction difficult. Therefore, it makes some sense to empirically administer magnesium to severely hypokalemic patients. Possibly the most vexing situation occurs when hypokalemia and acidosis coexist. Correction of acidosis aggravates the hypokalemia and often requires very aggressive K\(^+\) administration. In this uncommon situation, consideration should be given to the use of KHCO\(_3\) for replacement rather than the more common...
KCl. Alternatively, hemodialysis using a bath containing HCO\(_3\) and a higher K\(^+\) concentration is an effective treatment strategy.

As a general rule, K\(^+\) should not be infused more quickly than 20 to 40 mEq/h, and only in urgent circumstances. Infusion of potassium at this rate requires cardiac monitoring. Infusion into a peripheral vein is often painful; it occasionally induces chemical phlebitis, and if extravasated into soft tissue, it can cause necrosis. Rapid infusion of K\(^+\) into a central venous catheter terminating in or near the heart can result in arrhythmias. It is best to administer intravenous K\(^+\) diluted in non-glucose-containing solutions. (When glucose is coinfused, insulin release is stimulated, causing rapid incorporation of K\(^+\) into cells, which can potentially aggravate hypokalemia.) When possible, K\(^+\) deficits should be replaced with enteral preparations. One note of caution: if KCl solutions are repeatedly placed directly into the small bowel via feeding tube, irritation and even ulceration may develop.

Hyperkalemia

It is difficult for healthy subjects to develop hyperkalemia because even minimally functional kidneys efficiently excrete excess K\(^+\). Furthermore, when renal clearance decreases, the colon may increase excretion. Cellular buffering (particularly by muscle and liver) acutely blunts the impact of a K\(^+\) load while the kidneys eliminate the excess. Insulin deficiency inhibits cellular buffering, whereas excretion requires functioning kidneys. Therefore, K\(^+\) handling is greatly impaired in patients with diabetes and renal insufficiency. K\(^+\)-sparing diuretics (e.g., spironolactone), ACE inhibitors, ARBs, and, less commonly, nonsteroidal anti-inflammatory agents can induce hyperkalemia, especially in patients with baseline reductions in GFR or intrinsic renal disease.

Diagnosis

Pseudohyperkalemia may occur if venous blood is analyzed after prolonged tourniquet application or if the blood is hemolyzed. Serum K\(^+\) values are normally 0.5 mEq/L higher than the plasma values because K\(^+\) is released from platelets during clotting. However, marked hemolysis, severe leukocytosis (>100,000/mm\(^3\)), or thrombocytosis (>10\(^6\)/mm\(^3\)) also may raise the K\(^+\) of the clotted specimen to extraordinary levels. The diagnosis of clot-related “pseudohyperkalemia” is confirmed by detecting a disparity between simultaneous determinations of plasma and serum K\(^+\). Hemolysis can usually be confirmed by simple visual inspection of the sample.

Mechanisms

Three basic mechanisms contribute to hyperkalemia: (1) increased K\(^+\) intake, (2) redistribution of K\(^+\) from the intracellular to the extracellular compartment, and (3) decreased K\(^+\) excretion.

Even with the wide distribution of K\(^+\) supplements, hyperkalemia from excessive intake alone is uncommon. Likewise, iatrogenic K\(^+\) overloading often is seen in hospitalized patients with limited excretory power. Ringer solution contains 4 mEq/L of K\(^+\) and therefore should be administered carefully to patients with renal insufficiency. Potassium penicillin G contains 1.6 mEq of K\(^+\) for each 10\(^6\) units of penicillin, constituting a significant K\(^+\) load in patients receiving high penicillin doses. Packed red cells, stored for long periods, may
deliver more than 7 mEq/unit. Renal transplant recipients receive significant intraoperative K\(^+\) loads when donor kidneys perfused with Collins’ solution (140 mEq/L) are implanted.

Acidosis is the most common cause of redistributive hyperkalemia. Changes in serum K\(^+\) are more sensitive to changes in the bicarbonate concentration than to pH itself. Therefore, respiratory acidosis has relatively little influence on K\(^+\), whereas metabolic acidosis exerts a potent effect. Insulin stimulates intracellular transport of K\(^+\) from plasma; thus, when its deficiency leads to the development of ketoacidosis, two mechanisms redistribute K\(^+\) from cells to plasma. Digitalis toxicity poisons the cellular Na\(^+\)/K\(^+\) pump and may produce severe refractory hyperkalemia. β-Adrenergic blockers also can increase the serum K\(^+\) by blocking adrenergic-receptor-mediated cellular uptake of K\(^+\). Hyperkalemia may follow the breakdown of red blood cells from hemolytic transfusion reactions or from large hematomas. Any injury that produces extensive tissue necrosis can cause hyperkalemia, but rhabdomyolysis, crush injuries, burns, and tumor lysis are notable for doing so. Finally, succinylcholine (a depolarizing neuromuscular blocker) predictably produces a small rise in plasma K\(^+\) (approx. 0.5 mEq/L) but may precipitate striking hyperkalemia in patients with burns, tetanus, or other neuromuscular diseases.

Even though 80% to 90% of normal GFR must be lost before the kidney noticeably fails to excrete K\(^+\), renal insufficiency remains the most common cause of hyperkalemia. Among patients with renal insufficiency, concomitant drug therapy often is a complicating factor (Table 13-5). Acidosis induced by renal failure further impairs the ability of the kidney to excrete K\(^+\) and promotes the shift of K\(^+\) from cellular stores into the circulation. In renal failure of abrupt onset, serum K\(^+\) tends to rise faster than the BUN or creatinine, especially when exogenous K\(^+\) is given; low tubular flow rates immediately prevent exchange of Na\(^+\) for K\(^+\), whereas creatinine and BUN require time to accumulate to noteworthy concentrations. However, even when complete renal shutdown occurs, the serum K\(^+\) concentration seldom rises more than 0.5 mEq/L/day in response to the usual loads. (When normal K\(^+\) intake is exceeded or excessive release occurs from the damaged cells, this rate may be surpassed.)

Aldosterone is required to maintain circulating volume and to enable tubular secretion of K\(^+\). Therefore, primary adrenal insufficiency should be strongly considered in patients with hyperkalemia and prominent fluid deficits. Nonetheless, even with primary adrenal failure, significant hyperkalemia is unusual in the absence of another confounding factor (e.g., increased K\(^+\) intake or low GFR). Drugs that interfere with the formation or action of aldosterone (e.g., potassium-sparing diuretics, heparin, and ACE inhibitors and ARBs) also may produce overt hyperkalemia, especially as GFR declines.

Table 13-5. Drugs Associated with Decreased Renal Potassium Excretion

<table>
<thead>
<tr>
<th>Drug</th>
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<tbody>
<tr>
<td>ACE inhibitors</td>
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<tr>
<td>ARBs</td>
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<tr>
<td>Cyclosporine</td>
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<tr>
<td>Heparin</td>
</tr>
<tr>
<td>NSAIDs</td>
</tr>
<tr>
<td>Potassium-sparing diuretics</td>
</tr>
</tbody>
</table>
**Signs and Symptoms**

Hyponatremia, hypocalcemia, hypermagnesemia, and acidosis potentiate the neuromuscular effects of hyperkalemia. Therefore, levels of Na⁺, calcium, and magnesium should be evaluated and corrected concurrently. Functional impairment of skeletal muscle rarely occurs at K⁺ levels less than 7.0 mEq/L. Hyperkalemia usually spares the respiratory muscles, cranial nerves, and deep tendon reflexes but commonly causes weakness of the proximal lower extremities. The most devastating effect of hyperkalemia is cardiac arrhythmia; however, the myocardial-impairing and vasodilatory effects of severe hyperkalemia may precipitate refractory hypotension.

An electrocardiogram (ECG) should be obtained for every patient with a K⁺ more than 5.5 mEq/L (Fig. 13-2). Narrowing and peaking of T waves and QT interval shortening are typically seen with levels of 5.5 to 7 mEq/L. Lengthening of the PR interval and widening of the QRS complex (because of delayed depolarization) are often seen when concentrations reach 6.5 to 8.5 mEq/L. Atrial activity usually is lost shortly before the characteristic sine wave hybrid of ventricular tachycardia/fibrillation appears at levels greater than 8 mEq/L.

![ECG manifestations of hyperkalemia.](image)

**Treatment**

The aggressiveness with which hyperkalemia is treated should parallel the severity of the clinical expressions of the disorder—largely the ECG manifestations. When an elevated K⁺ develops in a patient with risk factors for hyperkalemia (e.g., renal insufficiency, tumor lysis, rhabdomyolysis) and significant clinical or ECG manifestations are present, immediate treatment is indicated. In situations that are less obvious or urgent, the diagnosis should be confirmed before initiating therapy because of the potential risk
of inducing hypokalemia if the initial high $K^+$ value is spurious. (A repeat $K^+$ determination, leukocyte and platelet counts, and an ECG should be obtained.) If the ECG is normal, treatment can usually await a repeat confirmatory $K^+$ determination. If the ECG is diagnostically abnormal, muscle weakness is present, or a reliable $K^+$ determination is more than 7 mEq/L, immediate action is indicated. Continuous ECG monitoring should be initiated, followed by treatment on five fronts as outlined in Table 13-6: (1) stop all $K^+$ administration, (2) expand intravascular volume, (3) begin removing $K^+$ from the body, (4) administer drugs to shift $K^+$ into the cellular compartment, and (5) stabilize neuromuscular and cardiac function with calcium.

<table>
<thead>
<tr>
<th>Table 13-6. Therapeutic Options for Hyperkalemia</th>
</tr>
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<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Intravenous saline (0.9% NaCl, 200-300 mL/h)</td>
</tr>
<tr>
<td>Action</td>
</tr>
<tr>
<td>Diluent</td>
</tr>
<tr>
<td>Enhances renal excretion</td>
</tr>
<tr>
<td>Onset</td>
</tr>
<tr>
<td>Minutes</td>
</tr>
<tr>
<td>Duration</td>
</tr>
<tr>
<td>Hours to days</td>
</tr>
<tr>
<td>Notes</td>
</tr>
<tr>
<td>Risks hypervolemia, hypernatremia, hypocalcemia, and hypomagnesemia</td>
</tr>
</tbody>
</table>

| Treatment                                         |
| Insulin (10 U regular), add one to two ampules D50W for normoglycemic patients |
| Action                                           |
| Enhances cellular uptake                         |
| Onset                                            |
| Minutes                                          |
| Duration                                         |
| Several hours                                    |
| Notes                                            |
| Risks hyperglycemia and hypoglycemia. Requires careful glucose monitoring |

| Treatment                                         |
| NaHCO$_3$ (one to two ampules over 5-10 min)      |
| Action                                           |
| Enhances renal excretion                         |
| Onset                                            |
| Minutes                                          |
| Duration                                         |
| Several hours                                    |
| Notes                                            |
| Risks hypervolemia, alkalosis, and hypernatremia. Probably effective only if urine alkaline |

| Treatment                                         |
| Nebulized $\beta$ agonist (albuterol)             |
| Action                                           |
| Enhances cellular uptake                         |
| Onset                                            |
| Minutes                                          |
| Duration                                         |
| Minutes to hours                                 |
| Notes                                            |
| Modest effect                                    |
| Risks tachyarrhythmias                           |

| Treatment                                         |
| Calcium gluconate (10-20 mL over 5 min)           |
| Action                                           |
| Membrane stabilizer                              |
| Onset                                            |
| Minutes                                          |
| Duration                                         |
| Minutes to hours                                 |
| Notes                                            |
| May induce hypercalcemia                          |

| Treatment                                         |
| Diuretics (furosemide 40-160 mg)                  |
| Action                                           |
| Enhances renal excretion                         |
| Onset                                            |
| Minutes                                          |
| Duration                                         |
| Several hours                                    |
| Notes                                            |
| Ineffective in renal failure                     |
| Risks volume depletion                            |
| Loop plus thiazide diuretic synergistic           |

| Treatment                                         |
| Dialysis                                         |
| Action                                           |
| Direct                                           |
| Onset                                            |
| Minutes                                          |
| Duration                                         |
| Hours to Hemodialysis most                       |
It is important to consider all potassium sources including standing orders for oral and IV supplementation and enteral and parenteral feedings. In patients who have intravascular volume depletion and those who are volume replete but can tolerate fluid administration, rapid infusion of isotonic saline can increase GFR promoting K⁺ excretion and will dilute the plasma K⁺ concentration. After achieving adequate intravascular volume, a loop diuretic can enhance excretion in patients making urine. Ion exchange resins lower K⁺ levels by trading Na⁺ for K⁺ across the bowel wall. (More Na⁺ is gained than K⁺ is lost, and electroneutrality is maintained by additional losses of magnesium and calcium.) Resultant Na⁺ gain may produce volume overload in oliguric or anuric patients. A typical 50-mg dose of resin decreases K⁺ levels by 0.5 to 1 mEq/L. When given orally, ion exchange resins require a vehicle to prevent constipation (usually 20% sorbitol solution). Dialysis is usually required for effective K⁺ removal from patients with renal insufficiency, severe hyperkalemia, or high K⁺ loads that result from multiple trauma or tumor lysis. Hemodialysis may extract 40 mEq/h or more, whereas peritoneal dialysis removes only 5 to 10 mEq/h.

Shifting K⁺ from blood into cells using insulin or β-2 adrenergic agonists rapidly lowers the serum concentration. A 10-unit intravenous bolus of regular insulin usually is sufficient to produce at least transient reduction in K⁺ levels. Patients with normal blood sugar levels should receive glucose (25 to 50 g) concurrently to prevent hypoglycemia. Insulin produces a reduction in serum K⁺ of 1 to 3 mEq/L within minutes, and it may last several hours. Nebulized β-2 adrenergic agonists have been shown to act synergistically with insulin to decrease K⁺ levels, but high doses or prolonged therapy is usually required. Nebulized albuterol (10 to 20 mg), which works by redistribution, has an onset within 30 minutes and remains effective for 2 to 5 hours. Cardiac rhythm should be monitored during this and other therapies.

Administration of sodium bicarbonate actually increases potassium excretion in the urine rather than shifting this cation into cells, as suggested by previous reports. Bicarbonate increases potassium excretion even in patients with relative renal insufficiency. Sodium bicarbonate infusion administered during 4 to 6 hours at a rate designed to alkalinize the urine may enhance urinary potassium excretion and be particularly desirable in patients with metabolic acidosis.

The major membrane stabilization agents are calcium (preferably given as calcium gluconate) and hypertonic saline. Electrocardiogram monitoring is important, particularly with calcium administration. Hypertonic saline appears to counter hyperkalemia by affecting the electrical properties of the myocardium.
rather than by reducing plasma potassium concentration. Because the efficacy of hypertonic saline therapy in patients with normal sodium levels has not been established, this intervention should be restricted to hyponatremic patients with hyperkalemia. When emergent intervention is required, calcium gluconate, insulin and glucose are most likely to produce timely benefit.

### CALCIUM DISORDERS

Normally each day approximately 1,200 mg of calcium (Ca$^{2+}$) is ingested, but only one third of that total is absorbed; renal excretion varies to balance serum levels between 8.5 and 10.5 mg/dL. Vitamin D serves to increase the gut absorption and renal tubular reabsorption of Ca$^{2+}$. Parathyroid hormone (PTH) also exerts significant influence over serum Ca$^{2+}$ balance by increasing the release of Ca$^{2+}$ from bone and promoting reabsorption of Ca$^{2+}$ in the distal renal tubule.

<table>
<thead>
<tr>
<th>Table 13-7. Causes of Hypercalcemia</th>
</tr>
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<tbody>
<tr>
<td><strong>Increased Gut Absorption</strong></td>
</tr>
<tr>
<td>Vitamin D or A intoxication</td>
</tr>
<tr>
<td>Milk-alkali syndrome</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Hyperparathyroidism (via increased Vitamin D levels)</td>
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Abnormalities in serum calcium occur commonly in critically ill patients. Depending on the specific patient population, hypocalcemia is found in 15% to 88% and hypercalcemia in approximately 15%. Only 1% of total body calcium is exchangeable with extracellular fluid, with the remainder of calcium residing in bone. Half of extracellular calcium is ionized in its physiologically active form, while considerable extracellular calcium is bound to protein, and the remainder is complexed with anions in calcium salts.

Total serum calcium is affected by changes in plasma protein concentrations, as approximately 40% of circulating calcium is bound to albumin. Direct measurement of serum ionized calcium is strongly advisable in patients with abnormal albumin concentrations. Ionized calcium concentrations are inversely related to plasma pH.

**Hypercalcemia**
Etiology

Although there is some mechanistic overlap, the long list of possible causes of hypercalcemia (Table 13-7) can be thought of as having three basic mechanisms: increased gut absorption, decreased renal excretion, or redistribution of Ca\(^{2+}\) from bone to serum. Relatively few disorders are responsible for most cases of hypercalcemia, and the list can be rapidly culled by taking a careful history and obtaining a few basic laboratory tests. Neoplasia and primary hyperparathyroidism together account for 80% to 90% of cases, with all other causes constituting the remainder. Specific malignancies include squamous cell cancer, breast cancer, myeloma, and renal cell carcinoma. Some tumors produce PTH-related peptide, which may stimulate hypercalcemia.

Thiazide diuretics, lithium, and tamoxifen are drugs associated with hypercalcemia. Hypercalcemia due to hyperparathyroidism is usually mild and only uncommonly causes significant intravascular volume depletion.

Signs and Symptoms

The signs and symptoms of hypercalcemia are nonspecific but most commonly result from the two major pathophysiologic derangements—dehydration and depressed neuromuscular function. Hypercalcemia induces an osmotic diuresis, but if fluid intake is unrestricted, severe Ca\(^{2+}\) elevations are unlikely. Unfortunately, the decreased gut motility of hypercalcemia often produces nausea, vomiting, abdominal pain, and constipation, negating this mode of compensation. The most common manifestations of hypercalcemia are neuromuscular disturbances (lethargy, weakness, fatigue, delirium, and coma).

Symptoms correlate poorly with Ca\(^{2+}\) concentrations, but severe manifestations are rare unless levels exceed 13 mg/dL. The ECG reflects the altered cellular electrical potential when it demonstrates a truncated QT or increased PR interval. Rarely, complete heart block occurs. Ca\(^{2+}\) salts form and are deposited in the tissue when a critical calcium-phosphate product (usually >60) is reached. In the kidney, renal stones and renal insufficiency may result from these complexes; skin deposits may induce pruritus. Muscle and other soft tissue may also be affected by this “metastatic” calcification. Pancreatitis or peptic ulcer diseases are less common presentations. Hypercalcemia may produce hypertension by increasing the peripheral vascular resistance, an effect that is usually offset by significant volume depletion.

Laboratory Evaluation

Ca\(^{2+}\) is predominately an extracellular cation, and because as much as one half of the total serum Ca\(^{2+}\) is bound to proteins (predominately albumin), Ca\(^{2+}\) levels must be evaluated in light of the serum protein level. For example, hyperproteinemic states such as myeloma can raise the total serum Ca\(^{2+}\) levels. Vulnerable to dietary influences, the serum PO\(_4\(^{3-}\)\) level is a highly labile measurement but, normally, an inverse relationship exists between the serum PO\(_4\(^{3-}\)\) and Ca\(^{2+}\). When this usual relationship is violated and both serum Ca\(^{2+}\) and PO\(_4\(^{3-}\)\) levels are elevated, vitamin D-related disorders and thyrotoxicosis are likely causes. PO\(_4\(^{3-}\)\) levels are usually low in primary hyperparathyroidism and malignancy. Urinary Ca\(^{2+}\) usually is very high in hypercalcemic disorders that are not dependent on PTH activity (i.e., sarcoid or vitamin D intoxication). Vitamin D levels are useful in confirming suspected toxicity but are not diagnostic in any other form of hypercalcemia. Although frequently assayed, PTH levels are not helpful diagnostically unless markedly elevated in a patient with severe hypercalcemia and normal renal function.
**Treatment**

Initial therapy for hypercalcemia includes administration of isotonic saline at 200 to 300 mL/h to correct intravascular volume depletion. After rehydration, furosemide (20 to 200 mg to avoid volume overload and enhance urinary calcium excretion) is given if GFR is greater than 30 mL/min. Zoledronic acid (4 mg as a 15-minute infusion) or pamidronate (60 to 90 mg as a 1- to 2-hour infusion) may be given if hypercalcemia persists after hydration. Salmon calcitonin (4 IU/kg) given subcutaneously or intravenously over 12 hours may be administered until bisphosphonates (above) take effect. Hydrocortisone (200 to 300 mg/IV) or prednisone (20 to 40 mg) is appropriate if hypercalcemia is caused by hematologic malignancy or granulomatous disease. Hemodialysis is appropriate for serum Ca$^{2+}$ greater than 14 mg/dL or in patients with impaired renal function or heart failure due to volume overload.

In general, mild hypercalcemia corrects with hydration. Bisphosphonates are generally added for treatment of hypercalcemia related to malignancy. If the estimated creatinine clearance is 30 to 60 mL/min, the dose of zoledronic acid should be reduced, and the drug is not recommended if creatinine clearance is less than 30 mL/min. A reduced dose of pamidronate is also recommended when creatinine clearance is less than 30 mL/min. Bisphosphonate-induced hypocalcemia is seen more frequently when these agents are used in the short term for treatment of conditions such as hypercalcemia from malignancy. In contrast, hypocalcemia is less frequent when bisphosphonates are used to treat osteoporosis. Salmon calcitonin reduces calcium levels within 2 hours of administration unlike bisphosphonates, which require 48 hours to achieve peak effect. Calcitonin is generally well tolerated and can be used in patients with congestive heart failure and azotemia where aggressive hydration may not be appropriate. Finally, corticosteroids effectively treat hypercalcemia caused by granulomous disease and hypercalcemia of hematologic malignancy by inhibiting proliferation of inflammatory cell activity and decreasing levels of 1,25-OH$_3$D.

Onset of action for hydrocortisone or prednisone is 3 to 5 days.

---

**Hypocalcemia**

Mild hypocalcemia occurs commonly during acute illness even in the absence of causative drugs, but it is rarely symptomatic. Overt hypocalcemia is less common than symptomatic hypercalcemia but is also life threatening. The urgency of evaluation and treatment depends on the severity of symptoms.

**Clinical Manifestations**

Hypocalcemia usually is asymptomatic if ionized Ca$^{2+}$ remains normal despite low total Ca$^{2+}$ levels, especially if hypocalcemia develops slowly. Alkalosis lowers the fraction of ionized Ca$^{2+}$, aggravating the symptoms. At normal pH, the usual threshold at which symptoms develop in hypocalcemia is 0.7 mg/dL for ionized calcium and 7.5 mg/dL total calcium; most symptoms are due to neuromuscular irritability. The most common complaints are paresthesia, cramps, or tetany. Dyspnea or stridor may occur if ventilatory or upper airway muscles are affected. Tetany also may develop. Rare but more specific signs of neuromuscular irritability, including carpopedal spasm (Trousseau sign) or facial muscle hyperreflexia (Chvostek sign), may be elicited in patients with hypocalcemia. Other potential CNS effects include seizures, hallucinations, confusion, and depression. In humans, the relationship between hypocalcemia and impaired circulatory system performance is reduction in perfusion by lowering the systemic vascular resistance and decreasing the cardiac contractility. The QT prolongation seen with hypocalcemia may result in a variety of arrhythmias (most significantly, torsades de pointes).

**Causes**
There are four mechanisms of hypocalcemia: (1) decreases in serum protein concentration, (2) binding and sequestration of Ca\(^{2+}\), (3) inability to mobilize bone Ca\(^{2+}\), and (4) decreased Ca\(^{2+}\) intake or absorption. Because most Ca\(^{2+}\) is bound to the serum proteins, reductions in protein concentration result in hypocalcemia. A reduction in albumin of 1 g/dL reduces the serum Ca\(^{2+}\) level by approximately 0.8 mg/dL. Ca\(^{2+}\) may be removed from the circulation by binding to other drugs or chemicals such as phosphate, chelating agents (e.g., ethylenediaminetetraacetic acid [EDTA]), or the citrate anticoagulant used to prevent the clotting of dialysis circuits or transfused blood. Ca\(^{2+}\) may also bind inflamed intra-abdominal fat in pancreatitis. Hyperphosphatemia induces hypocalcemia in patients with renal failure or in those who are otherwise unable to excrete \(\text{PO}_4^{3-}\) normally. Reductions in Ca\(^{2+}\) intake or impaired absorption resulting from reduced activity of vitamin D also may induce hypocalcemia. Anticonvulsants and glucocorticoids impair Ca\(^{2+}\) absorption (probably by inhibiting vitamin D action). Although renal failure decreases vitamin D production, symptomatic hypocalcemia usually is prevented by the development of secondary hyperparathyroidism. PTH deficiency and resistance to PTH are rare causes of hypocalcemia, except in patients undergoing thyroid or parathyroid surgery. For such patients, life-threatening hypocalcemia may develop within hours of surgery. Therefore, monitoring postoperative Ca\(^{2+}\) assumes added importance after surgical procedures in the neck, which have the potential to injure the parathyroid glands. Magnesium (Mg) levels should be obtained in hypocalcemic patients because Mg is necessary for both PTH secretion and action. Hypocalcemia secondary to hypomagnesemia is particularly common in alcoholics and in malnourished patients and those receiving diuretics. The causes of hypocalcemia are outlined in Table 13-8.

Table 13-8. Causes of Hypocalcemia

<table>
<thead>
<tr>
<th>Cause</th>
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<tbody>
<tr>
<td>Alkalosis</td>
</tr>
<tr>
<td>Anticonvulsant use</td>
</tr>
<tr>
<td>Citrate</td>
</tr>
<tr>
<td>Dialysis anticoagulation</td>
</tr>
<tr>
<td>Massive transfusion</td>
</tr>
<tr>
<td>Foscarnet</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
</tr>
<tr>
<td>Burns</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
</tr>
<tr>
<td>Renal failure—chronic</td>
</tr>
<tr>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Severe sepsis</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
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</tbody>
</table>

Treatment
The first step in the treatment of hypocalcemia is to ensure airway patency and adequate ventilation and
perfusion. Serum levels of K^+, Mg, vitamin D, and PTH should be obtained. Alkalosis should be corrected to raise the ionized Ca^{2+} fraction. In non-emergent settings, hyperphosphatemia should first be corrected with binders and a low PO_4^{3-} diet, preferably before administering Ca^{2+}. Ca^{2+} administration in the setting of profound hyperphosphatemia is unlikely to correct the defect because calcium phosphate salts will rapidly deposit in tissues. Ca^{2+} replacement is always empiric because deficits are impossible to calculate accurately. Therefore, correction must be guided by serial determinations of ionized Ca^{2+} and resolution of symptoms. Symptomatic patients should be given intravenous Ca^{2+}, preferably via a large central vein because of the tendency of Ca^{2+} solutions to induce chemical phlebitis or tissue necrosis when given in peripheral veins. Intramuscular injection should be avoided. Slow infusion of calcium gluconate or calcium chloride until symptoms resolve is the preferred method of supplementation. Concomitant vitamin D deficiency should be treated. Management of hypocalcemia is dictated by magnitude of deficiency and clinical impact. In general, symptoms occur below ionized calcium concentrations of 0.7 mg/dL or total serum calcium concentrations of 7.5 mg/dL. Short-term therapy is intended to reverse clinical effects rather than normalize serum calcium levels. Emergent therapies are needed in the setting of seizures and tetany. For severe symptomatic hypocalcemia, administer 10 to 20 mL of 10% calcium gluconate or 10 mL of 10% calcium chloride intravenously over 10 minutes and repeat every 60 minutes until clinical manifestations resolve. Avoid bicarbonate or phosphate administration during calcium administration. For moderate to severe hypocalcemia (ionized calcium < 1 mg/dL) without seizures or tetany, administer calcium gluconate 4 g/IV over 4 hours. Mild hypocalcemia (ionized calcium 1 to 1.2 mg/dL) is treated with calcium gluconate 1 to 2 g/IV over 4 hours. Assess progress with ionized calcium determinations.

In general, calcium gluconate is the preferable intravenous agent because it is less phlebitic and, thus, less likely to cause tissue injury or necrosis if extravasation occurs. Hypomagnesium must also be corrected if present. Patients receiving calcium, particularly those on digoxin, should have cardiac monitoring to reduce the risk of adverse cardiac events that include asystoli. Patients receiving digoxin should also be monitored closely for digitalis toxicity precipitated by calcium replacement. Hemodialysis is an option in patients with renal failure. In the setting of hypocalcemia and hyperphosphatemia, a phosphate binder should be administered along with calcium infusion to reduce the calcium times phosphorus product and the risk of calcium phosphate precipitation in tissues.

PHOSPHATE DISORDERS

Phosphate (PO_4^{3-}) and Ca^{2+} coexist in the body in a complex inverse relationship. As PO_4^{3-} levels rise, serum Ca^{2+} concentrations decline and vice versa. The bulk of both ions is located in bone; hence, the treatment of hypocalcemia is often an intervention directed at lowering PO_4^{3-} concentrations.

Hyperphosphatemia

In general, hyperphosphatemia is attributable to acute phosphate loading, extracellular shifts of phosphate, acute or chronic kidney disease, or primary increase in tubular phosphate reabsorption. Because of the huge excess capacity of the normal kidney to excrete PO_4^{3-}, it is difficult to become hyperphosphatemic (>5 mg/dL) from increased intake alone. Vitamin D intoxication can cause hyperphosphatemia by enhancing GI absorption of PO_4^{3-} and increasing tubular reabsorption of PO_4^{3-} in the kidney, especially if intake is high. Deficiency of PTH impairs renal PO_4^{3-} excretion, but it is alone a rare explanation for hyperphosphatemia. In the ICU, high levels of
PO$_4^{3-}$ usually reflect impaired excretion (i.e., renal insufficiency with GFR < 25 mL/min) with or without increased cellular release of PO$_4^{3-}$ (e.g., rhabdomyolysis, hemolysis, tumor lysis, etc.). Symptoms, however, are few, apart from those of hypocalcemia induced by excess PO$_4^{3-}$. In treating hyperphosphatemia, attention should first be directed to the primary cause of PO$_4^{3-}$ elevation. In addition, it makes sense to minimize PO$_4^{3-}$ intake. If renal function is intact, phosphate excretion is enhanced by saline infusion, but hypocalcemia may worsen. Where hyperphosphatemia represents a chronic condition, such as in chronic renal failure, a low-phosphate diet and phosphate binders are employed. In cases where hyperphosphatemia is causing severe hypocalcemia, dialysis may be required.

**Hypophosphatemia**

As the major intracellular anion, PO$_4^{3-}$ plays an important role in lipid, protein, and sugar metabolism. Serum values imperfectly reflect the depletion of intracellular PO$_4^{3-}$ stores responsible for clinical symptomatology. Although PO$_4^{3-}$ is easily depleted from skeletal muscle and erythrocytes, levels tend to be well preserved in most other tissues, such as cardiac muscle. Hypophosphatemia results from impaired intake, increased GI or renal losses, or uptake by cells. Hence, malnutrition and alcoholism are major risk factors. Low levels of vitamin D tend to decrease PO$_4^{3-}$ absorption and increase renal losses. Likewise, hyperparathyroidism increases renal excretion of PO$_4^{3-}$. GI losses (starvation, antacids, malabsorption, nasogastric suctioning, emesis, diarrhea, etc.) are contributing factors. Renal losses from tubular dysfunction or more commonly from diuretics (loop, thiazides, and osmotic) are also prevalent. Extracellular to intracellular transfer of PO$_4^{3-}$ occurs during anabolism, with insulin administration, during correction of metabolic acidosis, and in the acute phase of respiratory alkalosis. In the ICU, hypophosphatemia is commonly observed in alcoholics, during refeeding of the malnourished, during recovery from diabetic ketoacidosis, and during hyperventilation. In many such patients, hypophosphatemia is transient and does not reflect pathological PO$_4^{3-}$ depletion.

As a rule, serum PO$_4^{3-}$ must fall below 2.0 mg/dL before symptoms develop. Dysfunction of the cellular elements of the blood, muscle weakness, GI upset, neural dysfunction, and (rarely) tissue breakdown are the major clinical consequences and are typically seen if serum values fall below 1.0 mg/dL. Depletion of 2,3-diphosphoglyceric acid (2,3-DPG) diminishes the ability of erythrocytes to unload oxygen to the tissues. Skeletal muscle dysfunction can rarely produce ventilatory failure or prolonged weaning. A sensorimotor neuropathy is occasionally observed 4 to 7 days after PO$_4^{3-}$-poor nutrition is started. Very rarely, severe PO$_4^{3-}$ depletion can produce hemolysis, rhabdomyolysis, or congestive cardiomyopathy, especially when generous feeding is abruptly initiated in severely malnourished patients (the “refeeding syndrome”).

Oral supplementation usually will suffice when the serum PO$_4^{3-}$ is modestly reduced (>1.5 mg/dL). In general, 1,000 to 4,000 mg of phosphorus are given in divided doses to reduce incidence of diarrhea. Caution is advised because PO$_4^{3-}$ administration is accompanied by additional Na$^+$ or K$^+$, depending upon the product. Concurrent hypomagnesemia must be corrected for optimal effect. Oral PO$_4^{3-}$ supplementation should continue until reestablishing a serum level in the high normal range. Urgent correction should be reserved for situations in which clinical symptoms accompany serum PO$_4^{3-}$ levels less than 1.5 mg/dL. Where signs or symptoms of hypophosphatemia are present, replete phosphorus with parenteral preparations providing 2.5 to 5 mg/kg over 6 hours. Sodium and potassium loading may complicate parenteral therapy.
MAGNESIUM DISORDERS

Of the roughly 25 g of magnesium (Mg) present in the human body, more than 95% is intracellular (most in bone and muscle). Thus, similar to K⁺, large Mg deficits exist before hypomagnesemia becomes evident and administration of Mg transiently increases the levels in the relatively small intravascular space even though intracellular deficits may persist. In contrast to K⁺, Mg in blood is protein bound; hence hypoalbuminemia can reduce serum levels even when total body stores are adequate. To further complicate matters, the kidney is exquisitely effective in excreting Mg when plasma levels rise above normal. To highlight this fact, each day the average human ingests approximately 30 mEq of Mg, of which only 10 mEq is absorbed, and promptly, the kidney excretes 9.5 mEq and the gut eliminates the remainder. Despite the high frequency of abnormal serum Mg values, clinical manifestations of hypermagnesemia or hypomagnesemia are uncommon.

Hypermagnesemia

Under normal circumstances, the gut and kidney work in concert to tightly regulate serum Mg levels. When deficient, gut absorption of Mg increases and renal excretion decreases. When a larger enteral Mg load is presented, the gut absorbs a smaller fraction and the kidney excretes a greater proportion. Therefore, hypermagnesemia is uncommon unless very large intravenous doses of MgSO₄ are infused for preeclampsia or Mg salts are given to patients with renal insufficiency. (For patients with severe renal insufficiency or ileus, gut absorption of Mg-containing cathartics may overload the excretory capacity.)

Clinically, hypermagnesemia presents as hyporeflexia and hypotension when levels exceed 4 mEq/dL, somnolence develops at levels greater than 7 mEq/dL, and heart block and paralysis present at levels greater than 10 mg/dL. Hypermagnesemia prolongs the PR interval on ECG, impairs conduction, and may produce heart block. Initially, calcium gluconate (1 to 2 g intravenously) should be administered to counter neuromuscular effects. If renal function is preserved, administration of isotonic saline and loop diuretics can facilitate Mg excretion. Emergent dialysis is usually necessary because hypermagnesemia is rarely seen in the absence of severe renal insufficiency. Patients with hypermagnesemia, intact renal function, and no evidence of hemodynamic compromise may be treated by stopping exogenous magnesium and volume resuscitation.

Hypomagnesemia

Hypomagnesemia is one of the most common electrolyte abnormalities in hospitalized patients. Its common causes are presented in Table 13-9.

Hypomagnesemia can result from inadequate intake, increased GI or renal losses, or movement into cells. (Excessive renal or GI losses are most common.) Because Mg is predominately absorbed in the small bowel, inflammatory bowel disease, chronic diarrhea, and malabsorption are common precipitants. Hypomagnesemia, from poor intake and increased renal and gut losses, is particularly common and important in alcoholics because Mg is a required cofactor for the action of thiamine. Although several types of renal disease may produce Mg wasting, it most commonly results from the use of diuretics (thiazides, loop, and osmotic). The osmotic diuresis produced by the glycosuria of diabetes is a common precipitant. “Forced saline diuresis” also may waste Mg during cancer chemotherapy or treatment of hypercalcemia or rhabdomyolysis. Numerous conditions that transport Mg from plasma into the cells produce hypomagnesemia (e.g., refeeding syndrome, tumor growth, rhabdomyolysis, and pancreatitis) Aminoglycosides, cyclosporine, foscarnet, pentamidine, amphotericin, platinum, and alcohol all cause renal Mg loss.

Table 13-9. Causes of Hypomagnesemia
Hypomagnesemia has also been associated with PPI use. In this setting, hypomagnesemia is refractory to standard oral and parenteral magnesium replacement. In general, high doses of magnesium must be administered when due to this cause. Magnesium and PTH levels quickly normalize after PPI cessation and remain stable once magnesium replacement is concluded. An H2 blocker may be safely substituted for gastrointestinal prophylaxis if necessary. The median time for magnesium to normalize is one week after discontinuation of a PPI. It remains unclear whether PPI-associated hypomagnesemia is dose related. No evidence of urinary magnesium wasting has been consistently identified in patients with PPI-induced hypomagnesemia.

By encouraging K\(^+\) egress from cells and Ca\(^{2+}\) release from bone, hypomagnesemia may slowly promote hypokalemia and hypocalcemia. Mg deficiency should be considered in patients with hypokalemia, hypocalcemia, and hypophosphatemia, especially if they are encountered together. Like hypocalcemia, hypomagnesemia causes neuromuscular irritability manifested as muscle cramps, increased reflexes, tremor, Trousseau and Chvostek signs, cranial nerve abnormalities, and even seizures. (Neuromuscular or cardiac effects rarely occur until serum Mg levels are <1.0 mg/dL.) Hypomagnesemia predisposes to almost all types of arrhythmias including **torsades de pointes** and those of digitalis toxicity. The ECG effects of hypomagnesemia are nonspecific and rarely diagnostic.

Plasma levels imperfectly reflect total body Mg stores and correlate even less well with ionized Mg levels. Mg is inexpensive, and for patients with normal renal function, it is safe, even in large doses. For asymptomatic hypomagnesemic patients, oral preparations usually are effective at raising the Mg level, but sometimes produce such severe diarrhea that hypomagnesemia actually worsens. If the oral route is chosen, 0.5 mEq/kg represents a good starting dose. In mildly symptomatic hypomagnesemia, 6 to 8 g of MgSO\(_4\) can be given IV each day. In life-threatening hypomagnesemic crises, MgSO\(_4\) (1 to 2 g) is given IV over 2 to 3 minutes, followed by 2 to 4 g every 15 to 30 minutes until cardiac or neuromuscular abnormalities abate. In life-threatening cases, daily replacement of 6 to 8 g of MgSO\(_4\) is usually required to replete body stores. (It is prudent to measure serum levels once or twice daily to assure hypermagnesemia does not result.) Rapid intravenous Mg infusions can produce hypotension and therefore should be avoided except in emergent circumstances.
SUGGESTED READINGS


Chapter 14
Blood Conservation and Transfusion

• Key Points
1. In hemodynamically stable, nonbleeding patients, reasonable target levels for hemoglobin are 7 to 9 g/dL and greater than 20,000/mm\(^3\) for platelets. Higher levels may be appropriate in patients actively bleeding or those at particularly high risk from anemia or hemorrhage.
2. Many transfusions can be avoided if careful thought is given to blood conservation measures, including lowering the transfusion threshold, limiting laboratory determinations to only those necessary, and minimizing the volume of blood withdrawn for testing.
3. Effective use of blood components targets specific patient deficiencies and is a much more efficient use of the limited supply than use of whole blood.
4. Transfusion of blood that has been stored less than 2 weeks is associated with better clinical outcomes including fewer organ failures, shorter time in the ICU and on the ventilator, and lower rates of death.
5. Massive transfusion of the actively bleeding patient should be guided by frequent measurements of hemoglobin, coagulation parameters, and platelet counts. Although a robust literature supports massive transfusion as part of trauma resuscitation, comparable studies identifying best practice for other settings are not available.

INDICATIONS FOR BLOOD PRODUCTS
No blood is as good as your own. Setting aside concerns of transfusion-related infection and immune reactions, transfused blood is substantially less effective than native blood in its primary function of carrying O\(_2\) to tissues and leaving it there. In addition, receiving another’s blood is associated with the numerous risks outlined below, some of which are only partially understood. Therefore, unless absolutely necessary, it is not a good idea to receive allogeneic transfusion or perhaps even one’s own blood if it has been stored for more than several weeks. Despite the risks and limitations of transfusion, there are three situations in which blood products can be useful and even lifesaving: (1) to increase O\(_2\)-carrying capacity, (2) to reverse deficiencies of clotting factors, and (3) to correct thrombocytopenia.

Tissue oxygen delivery (DO\(_2\)) is the product of cardiac output, hemoglobin (Hgb) concentration, and O\(_2\) saturation. There normally is a trivial contribution from O\(_2\) dissolved in plasma. DO\(_2\) remains adequate even in the face of profound anemia (Hgb of 3 to 4 g/dL) if arterial saturation is normal and reductions in Hgb are offset by adequate increases in cardiac output and O\(_2\) extraction. Unfortunately, these compensatory mechanisms are often impaired in critically ill patients. For these reasons, Hgb concentration has traditionally been maintained greater than 10 g/dL, a value that corresponds to a hematocrit (Hct) ≥30%. By contrast, experimental evidence suggests that for most hemodynamically stable patients, substantially lower Hgb concentrations (approx. 7 g/dL) are not only tolerated but are also associated with better outcomes. Similarly, the lower acceptable limit for Hgb can be relaxed in patients with long-standing anemia and in those whose tissues and cardiac performance accommodate to chronically reduced O\(_2\) delivery (e.g., chronic renal failure). Maintaining traditional Hgb goals may be more important in patients with coronary or carotid ischemia, refractory hypoxemia, or limited cardiac reserve. Increasing Hgb, however, does not always increase DO\(_2\); as the Hct rises above 40%, increases in
viscosity eventually reduce overall DO$_2$ (Fig. 14-1). In addition, depletion of 2,3-DPG (diphosphoglyceric acid) in stored blood results in a leftward shift in the oxyhemoglobin dissociation curve, resulting in less tissue O$_2$ delivery than that of an identical concentration of native Hgb. Numerous other changes in stored red blood cells (RBCs), outlined below, further limit DO$_2$.

**FIGURE 14-1. Relationship between hematocrit, oxygen transport capacity, and serum viscosity.** At low hematocrit values, oxygen transport capacity (solid line) is impaired because of anemia. Oxygen transport increases with a rising hematocrit reaching a maximum value when hematocrit nears 35% to 40%. Transport capacity declines after this peak because of nonlinear increases in blood viscosity (broken line).

Administration of blood products solely to increase circulating volume is probably rational only in the setting of acute bleeding characterized by concomitant anemia and coagulopathy (e.g., massive hemorrhage in trauma or bleeding in the patient with hepatic failure or disseminated intravascular coagulation [DIC]). However, even in hemorrhagic shock, it makes sense to replace deficits with a combination of packed red blood cells (PRBCs) and crystalloid, unless massive losses necessitate supplemental plasma and platelet transfusion. In most settings, intravascular volume depletion can be corrected as quickly, with less risk and cost, using crystalloid solutions or nonblood colloid.
There are clear indications for treatment with clotting factors, where no other option will suffice. These situations include (1) bleeding from congenital or acquired isolated factor deficiencies; (2) hemorrhage because of multiple factor deficiencies from warfarin toxicity, hepatic failure, or consumptive or dilutional coagulopathy; and (3) correction of severe thrombocytopenia resulting in hemorrhage.

**ANEMIA**

Approximately one third of patients are anemic at the time of intensive care unit (ICU) admission, and nearly half develop anemia by the 3rd day in ICU. The majority of patients with an ICU stay exceeding a week receive a blood component, and of the transfused group, almost half receive more than 5 units of blood products. The incidence of anemia is understandable because many patients enter the ICU with subacute or chronic diseases and with RBC production blunted by functional iron deficiency and by decreased erythropoietin production and sensitivity. Critically ill patients are also subjected to intense phlebotomy that may outstrip limited production capacity.

**BLOOD PRODUCT CONSERVATION**

Because of stricter rules for donation, blood supplies are decreasing while demands are increasing. The good news is that donor selection and enhanced blood testing have made blood supply safer now than ever before with regard to traditional transfusion risks (e.g., viral hepatitis, human immunodeficiency virus [HIV]). Unfortunately, emerging data suggest that transfusions may be associated with heretofore underappreciated hazards (e.g., immune modulation). Furthermore, blood products are very expensive in many locations: a unit of PRBC may cost $1,000 or more. Because blood is increasingly scarce, expensive, and carries potential dangers, it makes sense to limit the need for its use.

Emerging data suggest that within broad limits, avoiding transfusion can shorten the length of stay and reduce organ failure rates. Attention to blood conservation during a protracted ICU stay reduces cost, risk of transfusion complications, and workload for nurses and laboratory personnel. Perhaps, half of all RBC transfusions could be averted if the volume and frequency of blood drawing were minimized, thresholds for transfusion were sensibly reduced, and erythropoiesis-stimulating agents were thoughtfully administered. Simple first steps to RBC conservation are the prohibition of “standing orders” for blood tests, reduced use of indwelling catheters, and whenever possible, use of alternative monitoring methods to minimize phlebotomy. Routine morning evaluations of chemistry and hematology panels and arterial blood gas determinations are unnecessary and wasteful for most patients. Blood test orders should be driven by clinical indication, not habit. Because they make obtaining samples easy, central venous and arterial catheters encourage sampling more frequently than is clinically necessary. Techniques such as bedside testing of blood glucose and the use of pulse oximetry and capnography to determine arterial O\textsubscript{2} and CO\textsubscript{2} tensions, respectively, can decrease bloodletting. ICU-based, small-volume, multichannel chemistry-blood gas analyzers can further reduce the quantity of blood used for monitoring as long as clinicians do not increase the frequency of testing because results are easy to obtain. Use of “cell savers” in trauma victims and in patients undergoing bloody surgical procedures is also prudent. Highly automated systems now collect shed blood from operative sites, mix it with an anticoagulant, wash the collected mixture, concentrate the RBCs, and then reinfuse them through a filter. For patients undergoing some elective operations, autologous transfusion is another technique to avoid donated cells.

Erythropoietin, darbepoetin, and comparable erythrocyte-stimulating agents (ESAs) comprise another element of an RBC conservation strategy. When administered just once a week, 40,000 units of recombinant human erythropoietin (rhEPO) has been shown to reduce the volume of RBCs transfused. Perhaps more importantly, about 10% of patients have avoided RBC transfusion altogether. Use of rhEPO requires the clinician to plan...
ahead; on average, a dose given today stimulates manufacture of the equivalent of roughly 1 unit of RBCs by next week provided that the marrow can respond. The lag time to produce results and the cost of rhEPO have been barriers to their deployment. One rational strategy for ESA use is (1) begin weekly ESA injections at the time of admission for most anemic, critically ill patients who are thought to be salvageable and likely to have at least a 7-day hospital stay (e.g., severe sepsis, acute respiratory distress syndrome [ARDS]); (2) at the time of admission, withhold ESA treatment from moribund patients, nonanemic patients, and those anticipated to have short ICU stays (e.g., asthma or chronic obstructive pulmonary disease [COPD] exacerbation, drug overdose, diabetic ketoacidosis); and (3) reassess the therapeutic plan at 4- to 7-day intervals. For example, it is reasonable to begin therapy for an anemic COPD patient initially thought likely to have a short stay but who develops nosocomial pneumonia and progressive anemia, or a patient initially believed to be moribund who rallies. Conversely, it is sensible to discontinue ESAs from a patient dying with inexorable multiple organ failure. When using ESAs, the target should not be a normal or supranormal Hgb, doing so is associated with a higher risk of complications including thromboses. ESAs may also extend the life of circulating RBCs.

The use of fresh frozen plasma (FFP) and platelets can also be sharply curtailed by knowing a few simple facts and making several safe, easy changes in practice. The first is recognizing that bleeding, either spontaneous or following procedures or surgery, is uncommon with platelet counts greater than 20,000/mm$^3$ and rare with platelet counts greater than 50,000/mm$^3$. Hence, unless the patient is bleeding or platelet function is known to be abnormal, withholding platelet transfusions until counts are less than 20,000/mm$^3$ (certainly <50,000/mm$^3$) does not usually compromise safety. (However, there are data to suggest that patients with consumptive coagulopathy may have a higher bleeding risk than patients with equivalent platelet counts without consumption.) Although not evidence based, some experts recommend maintaining periprocedural platelet counts greater than 50,000/mm$^3$ for patients undergoing surgery or invasive procedures, especially if bleeding would pose a high risk. The administration of platelets to thrombocytopenic patients with thrombotic thrombocytopenic purpura (TTP) or heparin-induced thrombocytopenia (HIT) may actually encourage thrombotic complications.

FFP is often administered to nonbleeding patients in an attempt to normalize a prolonged prothrombin time (PT) or activated partial thromboplastin time (aPTT), based upon the assumption that correcting the laboratory value will decrease the risk of bleeding. This practice is perhaps most common in patients presenting with excessive warfarin effect or hepatic failure but is also done for patients with DIC, vitamin K deficiency, or dilutional coagulopathy. Several observations suggest that this custom should be limited if not abandoned; only a minority of patients given FFP have in vitro clotting studies corrected, and the correction typically lasts only 2 to 4 hours. Perhaps, more fundamental is the fact that there is a poor correlation between modest PT and aPTT prolongations and risk of bleeding. Therefore, it makes sense to withhold FFP from nonhemorrhaging patients with PT and aPTT prolongations less than three times normal. When vitamin K deficiency, warfarin effect, or hepatic dysfunction are etiologic, administration of vitamin K can often correct in vitro clotting abnormalities in less than a day, at much lower cost and risk. (An exception to this guideline occurs in patients with significant elevation of INR from warfarin, in whom the risk of spontaneous bleeding is quite high. Prompt correction with FFP or clotting factor concentrates may warrant the additional risks and costs of administration.) A non-evidence-based and especially wasteful practice is the formulaic administration of platelets or FFP after a fixed number of red cell packs have been transfused.

**SOURCES OF BLOOD LOSS**

Because Hgb and clotting function measurements are sensitive to error and artifact, each time a physician is confronted with an abnormal value, the validity of the result should be questioned. Failure to do so will result in unnecessary diagnostic tests and transfusions. One should be particularly skeptical when abnormalities develop
suddenly and are large in magnitude, especially if they do not match the patient's clinical appearance. In stable patients with no “visible” blood loss, an acute decline in Hct of nine points or more (the equivalent of 3 units of RBCs) should make the laboratory result suspect. Similarly, sudden apparent “pancytopenia” with proportional decreases in white cells, red cells, and platelets is likely to indicate that the sample was obtained from a catheter and was diluted by infused fluid. As noted above, daily phlebotomy, which may cause loss of 40 to 70 mL of blood per day, should cause only a small fall in hemoglobin.

When convinced that abnormal laboratory data are accurate, it is important to carefully consider the cause of the abnormality. Simply stated, where did the blood clotting factors or platelets go? With few exceptions, it is difficult to rapidly lose substantial red cell mass without external evidence of blood loss. In the ICU, the most common sources of visible blood loss are the gastrointestinal tract or surgical and traumatic wounds. Because blood is an emetic and cathartic, rarely will large quantities of blood be “concealed” in the gut for long. When a true acute drop in Hct is not accompanied by obvious bleeding, retroperitoneal, rectus muscle, or thigh (soft tissue) bleeding; alveolar hemorrhage; and hemolysis should be suspected. Retroperitoneal bleeding may be spontaneous in patients with thrombocytopenia or soluble factor deficiencies or warfarin excess, but more commonly therapeutic anticoagulation and trauma (including femoral artery or vein cannulation or vena cava filters placement) are the causes. Soft tissues of the thigh can harbor large amounts of blood following femoral vessel puncture. Alveolar hemorrhage is most common in immunocompromised thrombocytopenic patients, occurring less often with Goodpasture disease, Wegener granulomatosis, or systemic lupus. Hemolysis may occur spontaneously, but in the ICU, it is more commonly drug or transfusion induced.

When production of platelets is diminished but consumption is not excessive, platelet counts usually decline slowly over 3 to 5 days. Therefore, sudden (<1 day) decreases in platelet counts are usually indicative of a consumptive process, often, for example, DIC or drug (e.g., heparin)-associated thrombocytopenia.

Similar to the situation with platelets, when production of soluble clotting factors is curtailed but consumption is not excessive, changes in the PT and aPTT times occur over several days. Rapid development of a coagulopathy is most likely related to accelerated factor consumption of sepsis-induced DIC or resulting from dilution of clotting factors by massive transfusion or resuscitation. The problems of thrombocytopenia and abnormal clotting studies are discussed at length in Chapter 30.

**THE COMPONENT SYSTEM**

Most patients receiving transfusions do not require all the components available in whole blood (Table 14-1). Component therapy “stretches” the blood supply by allowing prolonged storage of stable constituents and by permitting several patients to receive the specific components they need from a single donation. For example, RBCs are routinely stored for 5 to 6 weeks, and if frozen, can be stored up to 10 years. FFP can be stored for months, and purified clotting factors can be stored for years. The most time-limited component of blood is the platelet fraction, which lasts only days. By limiting administered volume, component therapy also reduces the risk of fluid overload, the amount of transfused anticoagulant, and the risk of infection.

**Table 14-1. Whole Blood Components**

| Erythrocytes          |
| Fresh frozen plasma   |
| Platelets             |
| Factor VIII concentrate |
Consequences of Blood Storage

In the 1970s and 1980s, some physicians insisted that their patients receive fresh whole blood because they believed better outcomes were achieved compared to use of component therapy. Advocates of the practice were often ridiculed because it seemed incredulous that giving whole blood could be any different than “remixing” just the needed components. Despite their advocacy, whole blood transfusion largely ended as the product became scarce, and with the rise of the AIDS epidemic, more dangerous. Two decades later, it is apparent that fresh whole blood may well have produced better outcomes, but we now know that important part of the equation was that the blood was fresh, not that it was whole. So what are the important differences between fresh and stored blood? Numerous abnormalities, collectively known as the “storage lesion,” have been identified in RBCs stored for two or more weeks. RBC rigidity, aggregation, and vessel wall adhesiveness are increased because of nitric oxide depletion and altered membrane lipid content. RBCs that lyse during storage release free Hgb, which neutralizes endothelial-bound nitric oxide causing vasoconstriction. Together, these changes impair capillary transit of RBCs. In addition, reductions in adenosine triphosphate (ATP) and 2,3-DPG inhibit tissue O\textsubscript{2} release by shifting the oxyhemoglobin dissociation curve leftward. The 2,3-DPG depletion persists for 1 to 2 days after transfusion. Because of metabolism of glucose in the storage media and spontaneous lysis of RBCs, the plasma portion of stored blood also contains higher levels of lactate, ammonia, potassium, and iron than fresh blood. Finally, inflammatory cytokines and microvesicles of shed RBC cell membranes increase in stored blood.

Red Blood Cell Components

Whole Blood

Whole blood can be used for emergent restoration of circulating volume and O\textsubscript{2}-carrying capacity, but unless fresh, it is a poor source of clotting components. (Platelets are nonfunctional within 24 hours; within 48 hours, essentially all factor VIII is depleted; and within a week, factors V and VII levels are negligible.) Furthermore, transfusion of whole blood may produce circulatory overload in the euvolemic patient who requires only RBCs (e.g., sickle cell disease, chemotherapy-induced anemia, myelodysplasia). A 500 mL “unit” of whole blood contains approximately 60 mEq of Na\textsuperscript{+} and has an average Hct of 35% to 40%. Whole blood is also more likely to contain microaggregates of leukocytes and platelets, which may be detrimental. The only remaining indication for whole blood is in support of massively bleeding patients, typically because of injury.

Packed Red Blood Cells

Removing the plasma from whole blood leaves a 200 to 300 mL unit of PRBCs having a Hct of 65% to 75%. PRBCs are used to restore O\textsubscript{2}-carrying capacity. One unit of transfused PRBCs should raise the Hct of an adult patient by approximately 3%. Continued bleeding or excessive volume expansion blunts the expected increase. PRBCs contain few platelets, clotting factors, or leukocytes and are not particularly effective as volume expanders when used alone. PRBCs can be infused as rapidly as whole blood when viscosity is reduced by adding approximately 75 mL of normal saline per unit.
PRBCs offer several advantages over whole blood: (1) less volume expansion for a given increase in O\textsubscript{2}-carrying capacity (each unit of PRBCs contains only 8 to 20 mEq of Na\textsuperscript{+}, a particularly helpful feature in patients with heart or kidney failure); (2) PRBCs contain less anticoagulant, reducing the potential risk of citrate toxicity; and (3) lower plasma volume, reducing the risk of allergy, anaphylaxis, viral hepatitis, and immunologic reactions from transfused antibodies. There are several disadvantages of using stored PRBCs: (1) there is a significant decrement in posttransfusion viability of the cells; (2) stored RBCs release K\textsuperscript{+} into the surrounding plasma as they age with concentrations often reaching 90 mEq/L; and (3) plasma ammonia concentrations rise.

**Specialized RBC Components**

Five processing methods are employed to improve the safety or longevity of RBCs (Table 14-2). Leukocyte-poor RBC transfusions are used in patients who have experienced white cell or leukoagglutinin reactions and for seronegative patients at-risk for cytomegalovirus (CMV) (CMV lives in white blood cells [WBCs]). Leukoreduction can be achieved by filtering, repeated washing, or freezing collected blood. Each method destroys some platelets while reducing the WBCs and plasma by approximately 75% to 90%. Because of the loss of RBCs in processing, a unit of leukocyte-poor RBCs contains less Hgb than a unit of PRBCs. Even leukocyte-poor RBCs contain small numbers of viable WBCs; therefore, blood products transfused into immunosuppressed patients must be irradiated to prevent graft versus host disease (GVHD). Even though it is probably a good idea to leukoreduce all RBCs, it is not done universally because the costs of doing so are prohibitive. At present, approximately 70% of RBC units in the United States are leukoreduced. Freezing or washing RBCs have additional advantages over filtration: the former two processes also minimize reactions caused by allergy to transfused proteins and those resulting from presence of anti-IgA or IgE antibodies.

<table>
<thead>
<tr>
<th>Processing Technique</th>
<th>Method</th>
<th>Purpose</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freezing</td>
<td>Glycerol preservation</td>
<td>Long-term storage of strategic blood supply and for rare blood types</td>
<td>Thawing and washing process are time consuming. Reduces but does not eliminate leukocytes</td>
</tr>
<tr>
<td>Irradiation</td>
<td>2,500 Gy exposure</td>
<td>Kill lymphocytes to prevent graft versus host disease in immunocompromised recipients</td>
<td>Time consuming, added expense. Does not reduce infection or allergy risk</td>
</tr>
<tr>
<td>Leukoreduction</td>
<td>Filtration</td>
<td>Reduction in WBC numbers to lower risk of febrile reactions, CMV, and alloimmunization</td>
<td>Does not prevent graft versus host disease</td>
</tr>
</tbody>
</table>
**Volume reduction**  
Plasma removal by centrifugation  
Reduce infused volume while preserving oxygen-carrying capacity  
Does not remove WBCs  
Less effective than washing to prevent allergic reactions

**Washing**  
Saline washing/centrifugation  
Removal of plasma proteins and electrolytes to deter allergic reactions and hyperkalemia

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**White Blood Cell Transfusions**

Because of the risk, expense, and questionable benefit of WBC transfusions, they are rarely used. WBC transfusions are considered only for neutropenic patients with overwhelming infections who fail conventional antimicrobial therapy. WBC transfusions are fraught with problems. Febrile and allergic reactions are nearly universal, and because WBCs have a circulating half-life of only 6 hours, frequent transfusion is required. WBCs must also be ABO compatible. Historically, hepatitis was commonly transmitted by WBC infusions, and CMV infection remains a risk. In patients with bone marrow depression, WBC transfusion also carries a nearly certain risk of GVHD. WBCs often aggregate, a tendency that precludes the use of transfusion filters and frequently leads to acute lung injury. At present, this therapy cannot be recommended.

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**Platelet Components**

**Random Donor Platelets**

The risk of hemorrhage rises as functional platelet concentrations decline, but thrombocytopenia must be marked before the risk of spontaneous bleeding increases significantly. The risks of bleeding are amplified at any given platelet concentration by concomitant abnormalities in platelet function, soluble clotting factor levels, and vascular integrity. Commonly used platelet counts to guide the need for transfusion are illustrated in Table 14-3.

Platelet concentrations greater than 50,000/mm³ are rarely associated with significant bleeding, even in trauma or surgical patients, and are more than sufficient to provide hemostasis in patients undergoing invasive procedures. Platelet counts less than 20,000/mm³ are associated with an increased risk of spontaneous hemorrhage (especially if counts fall below 5,000/mm³). Therefore, “prophylactic” transfusions are sometimes performed for counts in the 10,000 to 20,000/mm³ range, often undertaken with platelet counts of 5,000 to 10,000/mm³, and are almost always given when counts fall below 5,000/mm³. Practice is highly variable for non-bleeding patients when counts are in the 20,000 to 50,000/mm³ range. Even though the practice is not evidence based, patients with ongoing hemorrhage and those about to undergo invasive procedures in critical locations (e.g., intracranial surgery) are often given platelet transfusions, even when the levels are above 50,000/mm³. Regardless of number, platelet transfusions are also performed for therapy of platelet dysfunction because of uremia, liver disease, and nonsteroidal anti-inflammatory drugs in bleeding patients.

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**Table 14-3. Platelet Transfusion Guidelines for Nonbleeding Patients**

<table>
<thead>
<tr>
<th>Platelet</th>
<th>Spontaneous</th>
<th>Platelet Transfusion Given?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Platelets may be collected by centrifuging whole blood. A unit of pooled random donor platelets (RDPs) contains 40 to 70 mL of platelet concentrate and large numbers of WBCs that may be removed by filtration (leukoreduction). For each 5 to 6 units of transfused RPDs, patients receive roughly the equivalent of 1 unit of plasma. The usefulness of RDPs is limited by many factors: (1) repeatedly transfused patients develop alloantibodies to common platelet surface antigens and may eventually require human leukocyte antigen (HLA)-matched platelets to prevent rapid immune destruction of the transfused platelets; (2) platelet infusions often produce minor allergic reactions including chills, fever, and rash; (3) WBCs contained in platelet transfusions may produce GVHD in the immunocompromised patient; and (4) platelet transfusions are unlikely to be helpful and may be harmful in the “immune thrombocytopenias” (idiopathic thrombocytopenic purpura [ITP], TTP, or HIT) because of rapid platelet destruction. In such cases, plasmapheresis, corticosteroids, and intravenous immunoglobulin (IVIG) preparations may extend the circulating half-life of transfused platelets.

Platelets may be administered as rapidly as they will infuse (5 to 10 min/unit). The normal life span of circulating platelets is 3 to 4 days; therefore, platelet transfusions are usually needed every 2 to 3 days if production is reduced without accelerated destruction. There is some evidence that giving a larger dose less frequently results in fewer total transfusions than giving smaller doses more frequently. Each unit increases the count by 5,000 to 10,000 platelets/mm$^3$ unless destruction is ongoing. When assessed 1 hour after transfusion, an increment of less than 2,000/mm$^3$/unit confirms platelet destruction. Platelets are usually administered as “five-packs” or “six-packs,” which raise the platelet count by approximately 25,000 to 50,000 platelets/mm$^3$. A blunted increment is common in patients with burns, splenic sequestration, fever, severe sepsis, infection, and/or platelet antibodies. Because young (large) platelets have enhanced hemostatic function, the presence of many large platelets may indicate a lower risk of bleeding at any given count.

ABO compatible platelets minimize formation of antiplatelet antibodies and survive longer in the circulation. Because of the very small volume of plasma present in transfused platelets, incompatibility between donor plasma and recipient RBCs is usually insignificant. However, if multiple units of platelets and incompatible plasma are transfused, a positive Coombs test or overt hemolysis may occur. The small number of RBCs transfused in platelet concentrates makes RBC cross-matching unnecessary. (However, 10% of patients massively transfused with platelets will develop ABO sensitization.) Platelets do not contain Rh antigens, and

<table>
<thead>
<tr>
<th>Count (no./mm$^3$)</th>
<th>Bleeding Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5,000</td>
<td>High</td>
</tr>
<tr>
<td>5,000-20,000</td>
<td>Moderate to high</td>
</tr>
<tr>
<td>20,000-50,000</td>
<td>Low</td>
</tr>
<tr>
<td>50,000-100,000</td>
<td>Low</td>
</tr>
<tr>
<td>&gt;100,000</td>
<td>Low</td>
</tr>
</tbody>
</table>
therefore, Rh sensitization is not a problem. Although platelets should be administered through a filter to prevent aggregation, filtration lengthens infusion time and decreases the number of viable platelets transfused.

Platelets are the least stable blood component, requiring special handling and having a shelf life of just 5 days. To maintain functionality for even this length of time, platelets must be stored in plasma, constantly gently agitated (to maximize oxygenation) and maintained near room temperature. Unfortunately, this requirement dramatically increases the risk of bacterial proliferation in contaminated units. Current estimates suggest somewhere between 1 in 500 and 1 in 5,000 units of platelets are contaminated with bacteria. (Diphtheroids, coagulase-negative staphylococci, and other skin flora are the most common pathogens.)

**Single-Donor Platelets**

Most of the platelets transfused today come from single-donor apheresis and are HLA matched. Single donors may be pheresed as often as two or three times weekly to provide large numbers of platelets for transfusion. Administration of these pheresed concentrates (typically, approx. 300 mL) commonly produces a rise of 30,000 to 60,000 platelets/mm$^3$, roughly the increment seen with six random donor units. Single-donor pheresed platelets often transiently raise platelet counts, even if not HLA matched. In patients failing to respond to RDP or single-donor pheresed platelets, HLA-matched pheresed platelets usually will boost platelet counts. The effective survival of HLA-matched platelets can be nearly normal if used in patients alloimmunized to platelet antigens by random donor. However, if accelerated destruction is caused by non-HLA antigen mechanisms (e.g., DIC), HLA-matched platelets will not offer a substantial advantage over RDPs. Single-donor platelets have the advantage of reducing transfusion-related infection risk.

**Clotting Factor Concentrates and Plasma Products**

**Fresh Frozen Plasma**

Each 180 to 300 mL unit of FFP contains fibrinogen; clotting factors II, V, VII, VIII, IX, X, XI, XIII; and von Willebrand factor. Factors V and VIII and fibrinogen are present in the highest functional concentrations. FFP also contains donor antibodies and a substantial number of WBCs (even if the blood is leukoreduced at the time of collection). FFP is indicated to treat bleeding because of deficiency of multiple clotting factors, including (1) dilutional coagulopathy in the massively transfused patient, (2) excessive anticoagulation with warfarin, and (3) bleeding associated with hepatic synthetic failure.

FFP dosing is commonly guided by the severity of PT or PTT prolongation. In practice, PTs less than 18 seconds, INRs less than 1.5, and aPTTs less than 55 seconds are usually not treated unless patients are actively bleeding. The common practice of treating an elevated PT or aPTT less than three times normal in a nonbleeding patient is not evidence based. In cases where hemorrhage is ongoing, the end point of FFP administration is usually “normalization” of the PT and PTT. In most cases, factor levels of 25% to 30% of normal are sufficient to achieve hemostasis. Because humans have about 40 mL/kg of circulating plasma, a minimum of 10 to 15 mL/kg of FFP (2 to 4 units) is necessary to restore hemostasis in patients with profound deficiencies. Hence, if the decision is made to give FFP, it makes sense to administer at least 2 units, then reassess in vitro clotting times. Congenital or acquired coagulation factor deficiencies, including those of factors VIII and IX and von Willebrand factor, are better treated with specific concentrates of superior efficiency and safety. FFP should not be used primarily for intravascular volume expansion or as a source of albumin because less costly, equally effective alternatives exist.

FFP use has risks and several disadvantages: (1) each milliliter of transfused plasma contains only 1 unit of each clotting factor; therefore, relatively large volumes are needed to correct deficiencies compared to factor concentrates; (2) the risk of allergic (anaphylactoid) reactions is high because of plasma proteins and residual
platelets and leukocytes; (3) because FFP and other clotting factor concentrates have been common sources of viral infection in the past, they have been the targets of efforts to reduce viral contamination. Treatment with solvents and detergents has been shown to destroy enveloped viruses (i.e., HIV, CMV, Epstein-Barr virus, hepatitis B and C), but unfortunately, nonenveloped viruses (i.e., parvovirus, hepatitis A) are resistant to such treatments. The detergent process modestly reduces clotting factor concentrations (von Willebrand factor levels are affected most) and is expensive. Because RBCs and platelets are not routinely detergent treated, controversy exists as to the wisdom of using detergent-treated FFP in patients concurrently receiving nontreated blood products; and (4) FFP must be ABO compatible with the recipient's RBCs.

_Cryoprecipitate_

Cryoprecipitate forms when plasma separated from fresh whole blood is rapidly frozen and then allowed to rewarm. This small-volume (10 to 15 mL) extract contains most of the factor VIII (about 100 units), fibrinogen (200 mg), fibronectin, factor XIII, and 40% to 60% of the von Willebrand factor present in the original unit of plasma. Cryoprecipitate may be used to treat (1) hypofibrinogenemic states (e.g., thrombolytic therapy, congenital deficiency, and dilutional or consumptive coagulopathy), (2) factor XIII deficiency, (3) von Willebrand disease, and (4) hemophilia A (factor VIII deficiency). In hypofibrinogenemic states, 1 bag of cryoprecipitate/5 to 10 kg of body weight is a usual dose. When used for von Willebrand disease, 1 bag/10 kg is usually adequate. Because infection risk is now eliminated by using pasteurized or recombinant factor VIII, both these products are favored over cryoprecipitate for the treatment of hemophilia A. A role for cryoprecipitate may remain in the treatment of von Willebrand disease.

_Hemophilia Factor Replacement_

Because of the complexity of treatment, intensivists should seek help from coagulation specialists when treating hemophilia A or B and von Willebrand disease. Although FFP can be used to replace factor VIII or IX, it is an inefficient way to do so requiring large-volume infusions. The more concentrated cryoprecipitate reduces the required volume somewhat but is still suboptimal because of the risk of infection. Factor VIII concentrates solve this problem for patients with hemophilia A by pooling plasma of many donors (frequently hundreds) and then purifying the clotting protein using one of a variety of methods. Another, albeit more costly, option is the use of one of several recombinant human factor VIII products. For clotting factor replacement in patients with hemophilia B, monoclonal antibody purification of pooled plasma or recombinant factor IX is optimal, although prothrombin complex concentrates (PCCs) rich in factor IX may be used.

In the bleeding hemophiliac, either factor VIII or IX activity is negligible and should be increased to greater than 50% of normal levels to arrest hemorrhage. (Levels of 80% to 100% should be targeted for life-threatening bleeding and patients destined for the operating room.) The initial dose of clotting factor may be calculated by replacing 1 unit of factor VIII or IX per milliliter of calculated plasma volume per percent of desired factor activity. Because plasma volume is approximately 40 mL/kg, the simple calculation is given by this equation: dose (units) = 40 × (wt in kg) × (% factor activity desired). Because of a larger volume of distribution, higher doses of factor IX may be required.

Because administered factor VIII has a half-life of only 8 to 12 hours, close monitoring for clinical signs of bleeding and specific factor levels are necessary. The half-life of factor IX is longer (approx. 16 hours). Historically, factor VIII and IX concentrates carried a high risk of viral infection; however, careful donor selection and the institution of pasteurization, monoclonal antibody purification, microfiltration, detergent treatment, and serologic testing have all but eliminated the risk of viral hepatitis and HIV.

_Antithrombin Supplements_

Antithrombin (AT) concentrate is available for treatment of congenital AT deficiency and represents a preferable
alternative to use of large volumes of FFP. AT treatment of acquired deficiency states (e.g., sepsis) has been ineffective.

**Intravenous Immunoglobulin**

Although occasionally used for other indications, IVIG, a pooled immunoglobulin fraction from multiple donors, is useful in four distinct situations: (1) replacement therapy of humoral immune deficiency states such as congenital agammaglobulinemia, common variable immunodeficiency, and chronic lymphocytic leukemia; (2) control of selected infections such as streptococcal disease, staphylococcal sepsis, *Clostridium difficile* infection, and CMV infection with bone marrow transplant; (3) Guillain-Barré, acute myasthenia gravis, and other immune responsive neurologic conditions, and (4) treatment of ITP, TTP, and refractory thrombocytopenia because of repeated platelet transfusions. IVIG is not without risk; patients with immunoglobulin A deficiency may develop anaphylactic reactions from preformed anti-IgA antibodies, and antibody aggregates in IVIG may cause other allergic reactions. IVIG preparations may also transmit infections such as non-A, non-B hepatitis; however, the risk of HIV is very low.

**Recombinant Human Factor VIIa (rhVIIa)**

rhVIIa was developed as a treatment for hemorrhaging patients with hemophilia who had high titers of antibodies to either factor VIII or IX. It is also useful for treatment of inherited factor VII deficiency and may help in cases of antiplatelet antibodies causing refractory thrombocytopenia by initiating thrombin activation on the surface of platelets. The use quickly expanded well beyond these indications to include exsanguination from trauma, coagulopathy of liver failure, warfarin toxicity, and intracranial hemorrhage. Controlled clinical trials have now shown no survival benefit and little difference in amounts of transfused blood among trauma patients treated with rhVIIa compared to those given placebo. Likewise, formal study of rhVIIa in intracranial hemorrhage shows that the volume of bleeding is reduced but clinical outcomes are not improved. In non-hemophilia-related bleeding, clinicians should be dissuaded from the use of rhVIIa because of uncertainty about optimal dosing, lack of efficacy, extremely high cost, and anecdotal reports of clinical thromboses. If use of rhVIIa is considered, the expertise of a coagulation specialist should be sought.

Table 14-4. Prothrombin Complex Concentrates (PCCs) in United States

<table>
<thead>
<tr>
<th>Product</th>
<th>Coagulation Factors in Product</th>
<th>FCA-Approved Indications to Manage Hemorrhage</th>
<th>Heparin in Product?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonactivated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-factor PCC</td>
<td>Nonactivated II, IX, X, and small amounts of VII</td>
<td>Hemophilia B</td>
<td>No</td>
</tr>
<tr>
<td>Profilnine</td>
<td>Nonactivated II, IX, X, and small amounts of VII</td>
<td>Hemophilia B</td>
<td>Yes</td>
</tr>
<tr>
<td>Bebulin</td>
<td>Nonactivated II, IX, X, and small amounts of VII</td>
<td>Hemophilia B</td>
<td>Yes</td>
</tr>
<tr>
<td>4-factor PCC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kcentra</td>
<td>Nonactivated II, VII, IX, X, and proteins C and S</td>
<td>Warfarin</td>
<td>Yes</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------</td>
<td>---------</td>
<td>-----</td>
</tr>
<tr>
<td>Activated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feiba</td>
<td>Activated VII</td>
<td>Hemophilia A and B with inhibitors</td>
<td>No</td>
</tr>
<tr>
<td>Nonactivated II, IX, and X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Prothrombin Complex Concentrates (PCCs) (Table 14-4)**

PCCs are plasma-derived products containing factors II, VII, IX, and X. The 3-factor PCCs contain a minimal amount of factor VII. Table 14-4 shows the PCCs available in the United States. Of the available 4-factor PCCs, one contains factor VII primarily in the activated form (activated PCC). The other 4-factor PCC contains all of the vitamin K-dependent proteins (factors II, VII, IX, and X and proteins C and S). The 3- and 4-factor PCCs contain small amounts of heparin, which is insufficient to cause anticoagulation but contraindicates use of these products in patients with a history of HIT. Recombinant human factor VIIa initiates coagulation independent of tissue factor, factor VIII, and factor IX and is approved for use in patients with factor VII deficiency and hemophilia with factor inhibitors. PCCs provide replacement of functional vitamin K-dependent proteins to more rapidly reverse the anticoagulant effect of warfarin. The activated 4-factor PCC is approved for use in patients with hemophilia A and B with inhibitors. This product contains no heparin.

**PROBLEMS ASSOCIATED WITH MASSIVE TRANSFUSION**

**Exsanguination and Cross-Matching**

A formal cross-matching procedure requires 45 to 60 minutes. Therefore, when the patient's condition does not allow completion of a formal cross-match, O-negative (universal donor) or type-specific (ABO and Rh compatible) blood may be given. The small amount of plasma in O-negative blood often contains antibodies to the recipient's RBCs and can provoke delayed transfusion reactions. ABO determination alone usually takes less than 10 minutes. Therefore, type-specific blood is preferred except in cases in which transfusion must occur even more urgently.

**Massive Transfusion**

The rate at which blood products can be administered is proportional to the driving pressure for delivery and the fourth power of the IV catheter radius and is inversely proportional to the length of the IV catheter and viscosity of the fluid to be infused. Hence, using multiple (usually peripheral), short, large-bore IV catheters will usually be more efficient than smaller, longer, centrally placed catheters, except when large-bore introducer sheaths are already in place. Obviously, flow rates can be augmented by increasing the driving pressure through use of pressurized bags and high capacity blood warming systems. Fluid viscosity is rarely a limiting factor except when transfusing cold PRBCs. Viscosity can be dramatically reduced by warming the blood or by adding 100 to 200 mL of sterile isotonic saline to the PRBCs before infusion.

Massive transfusion is variably defined as the administration of greater than 10 units of blood (or 50% of the patient's blood volume) in less than 24 hours. Problems resulting from massive transfusion include (1) dilutional thrombocytopenia and coagulopathy, (2) alkalosis as $\text{PO}_4^{3-}$ is generated from transfused citrate, (3) hypocalcemia, (4) hypothermia, and (5) hyperkalemia.
In previously healthy persons, dilutional clotting disorders begin to emerge when one blood volume equivalent (5 to 10 units of blood) has been replaced. Clotting factor levels then commonly drop below 30% of normal, and platelet counts fall below 100,000/mm$^3$. Hence, after 5 units of blood have been transfused, platelet counts, PT, and an aPTT should be monitored.

There are limited high-quality data that address blood component use to manage major bleeding, particularly outside the realm of injury. When blood components were introduced into critical care practice, their benefit was never evaluated in randomized clinical trials. Retrospective studies of military casualties and of civilian populations have suggested improved survival with transfusion of 1 unit FFP for each unit of red cells given. This work encouraged earlier administration of an increased number of units of FFP and platelets. Despite the lack of solid evidence that bleeding after surgery and gastrointestinal or obstetric hemorrhage is associated with hemostatic changes similar to those seen in the trauma population, the early use of a transfusion ratio of FFP to red cells of 1:1 or 1:2 and liberal use of platelets have become commonplace. Following such policies, the incidence of transfusion-related acute lung injury (TRALI) and multiple organ dysfunction is increased.

Fibrinogen, however, is a critical tool in coagulation repair. It is the protein that ultimately forms fibrin, the ligand for platelet aggregation, and in patients with major bleeding, is required more any other hemostatic protein. In such patients, this requirement reflects increased consumption, loss, dilution, and fibrin breakdown. Thus, the trigger level for supplementing fibrinogen should be 1.5 to 2.0 g/L rather than a more traditional 1.0 g/L.

There are data to support the use of tranexamic acid in patients with major bleeding after trauma. This recommendation is supported by the large randomized CRASH-2 trial, which included over 20,000 injured patients in multiple countries with active bleeding or at risk for major bleeding. Patients receiving tranexamic acid within 3 hours of injury had mortality risk from bleeding reduced by one third. This benefit was lost, however, if the drug was given later than 3 hours after injury. The incidence of thrombosis after injury was not increased in study patients. Tranexamic acid has long been available for patients undergoing surgery and has reduced the need for blood transfusion in that setting. Although tranexamic acid should be considered in other patients with major bleeding who requires massive transfusion, trial data specific to most patient groups are not available.

RBCs are collected in an acidic environment (pH 7.1) using sodium citrate and citric acid as preservatives. As blood ages, the pH drops further because of the cellular production of pyruvate and lactate. Surprisingly, when transfused, this “acidic” solution does not cause acidosis in the absence of profound shock. To the contrary, when infused, each unit of blood yields 23 mEq of bicarbonate from the hepatic metabolism of citrate. If impaired kidney function limits bicarbonate excretion, metabolic alkalosis results. Similarly, in the presence of renal insufficiency, the K$^+$ challenge of PRBCs (up to 90 mEq/L) can induce hyperkalemia. If alkalosis occurs, serum K$^+$ and ionized Ca$^{2+}$ concentrations both may decline, but symptomatic hypokalemia is uncommon because of the K$^+$ in transfused PRBCs. Even during massive transfusion, the incidence of citrate-induced hypocalcemia is very low. (Typically, more than 10 to 20 units of PRBCs must be infused each hour to provide a citrate load sufficient to depress Ca$^{2+}$ levels.) Although replacement is rarely necessary, it is prudent to monitor calcium levels. If symptomatic hypocalcemia develops, administration of 10 to 20 mL of 10% calcium gluconate, or 5 mL of 10% CaCl$_2$, for each unit of PRBCs usually suffices.

Systemic hypothermia has numerous adverse effects (see Chapter 28), among the most important of which is inhibition of clotting enzyme activity. In the profoundly hypothermic patient, this can translate into a significant functional coagulopathy despite normal levels of clotting proteins. Blood warming is a reasonable practice with (1) massive transfusion, (2) transfusion rates exceeding 50 mL/min, or (3) cold agglutinin disease. Blood may
hemolyze if heated above 38°C.

**COMPLICATIONS OF TRANSFUSION**

Receiving blood products is now safer than it has ever been in the history of transfusion medicine; nevertheless, there are still numerous risks, the approximate frequencies of which are presented in Table 14-5. Conceptually, most complications can be thought of as either immunologic or infectious.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Risk per Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>1 in 800,000-1,200,000</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1 in 1,100,000</td>
</tr>
<tr>
<td>HIV</td>
<td>1 in 1,500,000</td>
</tr>
<tr>
<td>HTLV I and II</td>
<td>1 in several million</td>
</tr>
<tr>
<td>West Nile Virus (WNV)</td>
<td>Rare</td>
</tr>
<tr>
<td>Bacteria Detected</td>
<td>1 in 6,000 (platelets)</td>
</tr>
<tr>
<td></td>
<td>Rare (other components)</td>
</tr>
<tr>
<td>Bacterial Sepsis</td>
<td>1 in 100,000 (platelets)</td>
</tr>
<tr>
<td></td>
<td>Rare (other components)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>No transfusion-transmitted cases reported in last 40 years</td>
</tr>
<tr>
<td>Babesia spp.</td>
<td>Rare</td>
</tr>
<tr>
<td><em>Ehrlichia chaffeensis</em> and <em>Anaplasma phagocytophilum</em></td>
<td>Rare</td>
</tr>
<tr>
<td>Malaria</td>
<td>Rare</td>
</tr>
<tr>
<td>Acute Hemolysis</td>
<td>1 in 76,000</td>
</tr>
<tr>
<td>Fatal Acute Hemolysis</td>
<td>1 in 1,800,000</td>
</tr>
<tr>
<td>Delayed Hemolysis</td>
<td>1 in 2,500-11,000</td>
</tr>
<tr>
<td>Allergic Reaction</td>
<td>1 in 100-300</td>
</tr>
</tbody>
</table>
Immunologic Complications

**Febrile, Nonhemolytic Transfusion Reactions**

Febrile, nonhemolytic transfusion reactions are the most common transfusion-related adverse event. Febrile reactions are an immunologic response by the recipient to surface antigens on WBCs, or less commonly inflammatory cytokines in donor blood. Between 15% and 20% of RBC recipients develop fever during transfusion, but only a fraction of these cases are of sufficient magnitude that they are reported as a transfusion reaction. In the severe cases, flushing, fever, and chills are prominent within 60 minutes of starting the RBC infusion. In patients with previous febrile reactions, the use of leukocyte-poor RBCs and HLA-matched components reduce the risk.

**Allergic/Anaphylactoid Reactions**

Allergic reactions, ranging from mild urticaria to frank IgE-mediated anaphylaxis, occur with about 3% of RBC transfusions. Because such reactions are more common among IgA-deficient recipients, it has long been thought that the mechanism was preformed IgG recipient antibodies directed against IgA in donor blood. Data now suggest that recipient antibodies to haptoglobin also may be involved. Stopping the transfusion and administering antihistamines are usually sufficient to abort the reaction. Full-blown anaphylaxis should be treated with intravenous epinephrine and volume expansion. Inhaled β-adrenergic agonists may moderate bronchospasm. Despite widespread use of corticosteroids, they are not effective. To avert future episodes, blood products from IgA-deficient donors or washed RBCs or platelets are usually selected.

**Immediate Hemolytic Reactions**

Hemolytic reactions can be immediate or delayed. If immediate, they are usually because of major ABO incompatibility, the most common cause of which is misidentification of the patient sample or transfusion of properly matched blood into the wrong patient. As a result, stringent rules have been instituted in most hospitals requiring two licensed health care providers to check the blood product against patient identification to avoid this mistake. As a corollary when notified by the blood bank that they have received an improperly labeled sample, repeat collection is indicated. Fortunately, these mistakes are rare (1/10,000 to 1/100,000 transfusions) with fatalities even less common (1 per 10^6 transfusions). Although HIV and viral hepatitis are often cited by clinicians as the most concerning risks of transfusion, simple administrative or clerical error resulting in transfusion of blood into the wrong patient may be 10 to 100 times greater. Any process that causes lysis of the donor cells ex vivo (e.g., overheating, freezing, administration through a small-bore needle, or mixing RBCs with hypotonic fluid) can mimic an immunologic hemolytic reaction when those cells are infused.

Most severe reactions occur rapidly as the first 50 to 100 mL of blood is infused. For this reason, frequent vital signs should be taken in the initial period of transfusion. Major reactions are potentially fatal because they produce intravascular hemolysis, coagulopathy, shock, renal failure, and pulmonary dysfunction. New-onset anxiety, dyspnea, fever, back or infusion site pain, and diffuse bleeding are all clues to transfusion
reaction. (Such signs and symptoms may be difficult to recognize in the unconscious, critically ill patient.) Primary treatment of a major reaction is to stop the transfusion. Using sterile technique, donor blood and blood tubing should be returned to the blood bank. Clotted and anticoagulated samples of the recipient's blood and a urine sample should also be sent to the blood bank with notification of a suspected transfusion reaction. Fluids and vasopressors should be administered as required to maintain perfusion. Intravenous NaHCO₃ may be given to prevent precipitation of Hgb in the renal tubules and subsequent acute kidney injury. Loop and osmotic diuretics may also be useful to preserve urine flow and avert renal failure.

**Alloimmunization and Delayed Hemolytic Reactions**

Alloimmunization is common, occurring roughly once for each 100 transfused units; fortunately, delayed hemolytic reactions are much less common occurring in only 1/6,000 RBC transfusions. Low-titer alloantibodies (often undetectable by Coombs test) can cause delayed hemolysis in previously transfused or multiparous patients, as the transfused RBCs recall an amnestic response that produces IgG antibodies directed against donor cells. Over the next 10 to 14 days, antibody levels rise, the direct Coombs test becomes positive and transfused RBCs lyse resulting in a sudden (but often asymptomatic) drop in the Hct. Concomitantly, serum haptoglobin levels fall and lactate dehydrogenase levels increase. Although usually benign, a falling Hct and rising bilirubin, especially in a postoperative patient, may raise concerns of hepatic failure or occult bleeding.

**Transfusion-Related Acute Lung Injury (TRALI)**

Transfusion-related acute lung injury (TRALI) is a relatively common (1/1,200 to 1/5,000 transfusions) syndrome of acute lung injury, which promptly (within 1 to 6 hours) follows transfusion of RBCs or more commonly plasma. Typical manifestations are cough, dyspnea, and hypoxemia; one third of patients exhibit either hypotension or hypertension. The chest radiograph indicates noncardiogenic pulmonary edema. Although the mechanism remains debated, the observation that risk of the syndrome is highest with donations from multiparous women suggests that the cause could be donor alloantibodies to recipient leukocytes or plasma proteins. For this reason, some countries have adopted a policy of only transfusing FFP from men. The incidence of TRALI appears to be higher in older recipients. Treatment is supportive, similar to other forms of ALI, and the syndrome typically resolves more rapidly that acute lung injury of other causes.

**Graft Versus Host Disease (GVHD)**

Graft versus host disease occurs when donor T lymphocytes colonize the recipient, subsequently attacking the new host as foreign. GVHD was once believed to occur only in immunocompromised patients (e.g., following marrow ablative chemotherapy or radiation therapy), but it is now clear that normal hosts are also at risk. Manifestations range from subclinical microchimerism to minor skin and gut disease to death (rare). Because freshly collected blood contains higher numbers of viable lymphocytes, it poses a higher risk of GVHD; the risk is lowered by leukoreduction but can only be eliminated by irradiation of the donor blood to kill lymphocytes.

**Transfusion-Related Immune Modulation**

It has long been known that receiving preoperative allogeneic blood transfusions improved the survival of transplanted organs. However, although hotly debated, more recent observations suggest that patients receiving perioperative RBC transfusions are more prone to infections and recurrence of resected tumors, a process called transfusion-related immune modulation (TRIM).
Infectious Complications

**Bacterial Infections**

Bacterial infections transmitted through transfused blood are most frequently because of breaches in sterile technique at the time of the transfusion and to prolonged infusion time. When a contaminated blood component is to blame, platelets are the most likely source. (If contaminated when obtained from the donor, bacterial growth can proceed unabated because platelets must be stored at room temperature, without preservative.) It should be noted that *Listeria monocytogenes* is capable of growing at the usual storage temperature of RBCs and may cause transfusion-related bacteremia.

**Viral Infections**

Because of the large number of donors required for preparation, the risk of viral infection has been highest with pooled blood products (e.g., factor VIII concentrate and activated factor complexes). Better selection of donors and biochemical and serologic testing have reduced the prevalence of these infections in the donor pool. Processing of blood including filtration and treatment with solvents and detergents has dramatically reduced the risk of acquiring enveloped viruses (i.e., HIV, CMV, Epstein-Barr virus, hepatitis B and C), but unfortunately, nonenveloped viruses (i.e., parvovirus, hepatitis A) are still a problem because they resist treatments designed to inactivate them. Other infections potentially transmitted via blood include malaria, syphilis, brucellosis, and toxoplasmosis. Zika, for which a donor-screening test is now available, does not appear to present a significant risk.

Depending on the region of the country, screening tests for HIV have lowered the risk of transfusion-acquired AIDS infection with blood product administration. Currently available medical management has rendered HIV a chronic, treatable disorder. Hepatitis C is a more important contemporary concern.

Miscellaneous Complications

RBCs, WBCs, platelets, and cryoprecipitate should all be administered through standard blood filters to prevent transfusing aggregates of these components. All filters reduce the maximal infusion rate and should be changed after every 2 to 4 units because of filter plugging.

Hyperkalemia may occur in massively transfused patients, given that PRBCs are stored for long periods of time (especially patients with renal dysfunction). Potassium concentration may approach 90 mEq/L in the plasma transfused with packed cells stored more than 3 weeks. Hyperkalemia may be prevented by using fresh blood or by using RBC products containing little plasma, such as washed PRBCs.

Citrate-induced hypocalcemia has been touted as a problem in the massively transfused patient but is a rare event. Prophylactic administration of calcium is not recommended, but if the patient exhibits signs of hypocalcemia, determination of ionized calcium is warranted. Because sodium citrate is used to anticoagulate most blood components, alkalemia may develop as the liver converts citrate to bicarbonate. Patients with normal liver function are able to metabolize massive amounts of citrate (that contained in up to 20 units of PRBCs per hour). Therefore, metabolic alkalosis of citrate infusion is usually clinically insignificant and self-correcting.

**BLOOD SUBSTITUTES**

Extracted, purified, and stabilized Hgb and genetically engineered Hgb solutions continue to be investigated as blood substitutes but are not ready for clinical use. In the past, Hgb solutions have carried substantial risk of
renal tubular damage. Limited application of O₂-carrying perfluorochemical solutions in coronary reperfusion has shown promise in experimental settings, but there is no evidence supporting their safe and effective clinical use.

**SUGGESTED READINGS**


Chapter 15
Pharmacotherapy

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• Key Points
1. It is essential to review the medication list of every patient daily, preferably with a pharmacist specializing in critical care.
2. In choosing a cost-effective medication therapy, consider not only the direct cost of the drug but also the indirect costs including labor to prepare and administer the medication, nonpharmaceutical materials, and overhead, as well as drug interactions and potential adverse effects.
3. Cost savings can be achieved with strategies such as use of guidelines and protocols.
4. Pharmacokinetics and pharmacodynamics of medications change frequently in the critically ill patient because of rapid fluctuations in the underlying physiology. This makes drug dosing and predictability difficult.
5. Different routes of medication administration may be advisable in critically ill patients because of changes in volume status and the availability of unique methods of delivery.

QUALITY IMPROVEMENT AND COST CONTROL
The intensive care unit (ICU) is one of the hospital's highest consumers of pharmacy services and uses some of the most expensive (e.g., fomepizole, daptomycin, IVIG) and potentially dangerous (e.g., tissue plasminogen activator, four-factor prothrombin concentrates, insulin, argatroban) drugs. Because critically ill patients often receive 10 or more medications each day, the potential for dosing errors, drug interactions, and adverse events is high.

In addition, medication charges can account for a large part of the ICU bill. In one hospital study, ICU pharmacy charges accounted for more than 10% of total ICU charges. Although it can be argued that almost any cost for a truly “lifesaving” drug is justified, there are not many drugs that fit that description. Obviously, therapies known to be inferior should not be chosen just because they are less expensive, but careful deliberation often reveals that equally effective, less expensive alternatives exist.

Undoubtedly, medications represent a potential opportunity for savings, but drug costs are often unreasonably targeted. This happens, partly, because pharmacy is one of the few departments of the hospital that has any idea of acquisition costs, drug utilization data, and reimbursement. It is essential to interact and collaborate with key leaders from various departments to successfully plan, prioritize, and implement medication-cost management efforts. Of course, there are practical limitations to what can be accomplished. Consider the most extreme case where all medications are eliminated; even if such a practice did not worsen outcomes, such a radical change would only reduce costs by approximately 11%.

Role of the Pharmacist
Many studies indicate that having a pharmacist as part of the ICU team helps identify numerous potential opportunities for care improvement and cost savings. Cynically, some physicians believe that pharmacy
involvement is intended only to cut costs, but pharmacists often correct, clarify and reconcile conflicting orders, provide important drug information, suggest alternative therapies (especially in times of drug shortages), identify drug interactions, and provide therapeutic drug monitoring (e.g., vancomycin, warfarin). Regardless of the effect on cost, ample data indicate that when a critical care-trained pharmacist is included in rounds, pharmacotherapy is simplified, important treatments are initiated, drug-related adverse events decline, and medication errors are reduced. Unfortunately, some hospitals are reluctant to provide pharmacist support because quantifying savings from preventing a drug-drug interaction or an adverse event is often difficult.

Quality Improvement Strategies

Clinical pharmacists are trained to analyze the medication record, evaluating each medication for indication, efficacy, correct dosing, drug-drug interactions, and adverse effects. Daily review of the medication profile often reveals drug duplications (e.g., overlapping narcotics such as oxycodone and hydromorphone), unnecessary medications (e.g., stress ulcer prophylaxis without a clear indication), and competing medications (e.g., heparin and phytonadione). Daily review of the medication profile also commonly exposes drug-drug interactions (e.g., warfarin and sulfamethoxazole/trimethoprim or midazolam and fluconazole) and adverse effects (e.g., amphotericin B causing hypokalemia or a beta-lactam antibiotic such as piperacillin/tazobactam causing thrombocytopenia). The incidence of adverse effects is magnified by allowing multiple consulting physicians to write medication orders. Numerous ways in which medication practices can be improved are discussed below.

Use of Guidelines and Protocols

A fundamental step in improving medication safety is to establish guidelines and protocols (in written or electronic format) for medications that are frequently overlooked, may be used in excess, provide inadequate treatment, are difficult or dangerous to use, or are contraindicated for certain situations/disease states.

Guidelines or protocols help ensure appropriate ordering of prophylactic therapy. For example, patients at high risk for developing a stress ulcer should receive prophylaxis to prevent this, but they are not necessary for every patient in the ICU and may carry hazards of their own. Some physicians believe that stress ulcer prophylaxis with either an H2 blocker or a proton pump inhibitor is so inexpensive that using it for every ICU patient may be beneficial; however, this does not take into account potential drug-drug interactions (e.g., some concurrent drugs may need acid to be effective) or adverse effects (increased risk of thrombocytopenia, pneumonia, and possible *Clostridium difficile* infections). Hence, guidelines may provide criteria for selection of appropriate candidates.

Another important example is venous thromboembolism (VTE) prophylaxis. Without prophylaxis, VTE occurs so frequently in the critically ill that it makes sense to use preventative therapy in almost all patients, but doing so may be overlooked, especially when residents rotate or when physicians change patient assignments. An established and routinely reviewed guideline can help identify those patients who should receive chemical VTE prophylaxis and those in whom it may be inadvisable. In such cases, nonpharmacological alternatives such as intermittent compression by pneumatic devices should be preferred. The importance of VTE prophylaxis has been magnified now that funding and regulatory agencies hold hospitals responsible for potentially preventable thromboembolism.

To prevent excessive or inadequate treatment, it is also an excellent idea to develop guidelines for dosing medications to objective end points. Using a validated pain scale to guide opioid dosing can achieve better analgesia with fewer side effects. Sedation tools (e.g., Richmond Agitation Sedation Scale) with mandated drug interruptions have been shown to reduce total doses of administered drugs and to shorten the length of mechanical ventilation and ICU stay while lowering costs. The Clinical Institute Withdrawal Assessment of Alcohol (CIWA) scale offers yet another example. In this instance, quantification of symptoms is key to reducing...
length of stay and total benzodiazepine dose.

Protocols help ensure safe pharmacotherapy. Tissue plasminogen activator (tPA) and argatroban are examples of drugs that are both potentially dangerous and unfamiliar enough to pose practical problems. For patients with ischemic stroke, tPA is often given, and yet many nurses only use this medication a handful of times during their careers. Because of its high risk for bleeding, it is beneficial to have a protocol for nurses to follow, as tPA must be administered in a very specific time frame and manner. Argatroban is usually only used in patients with suspected or confirmed heparin-induced thrombocytopenia who have a need for therapeutic anticoagulation; therefore, both nurses and physicians are likely to use this medication rarely. Again, because of its high bleeding risk, it is beneficial to have an established guideline to prevent complications as well as treatment failures.

Protocols or guidelines should be in place for medications used in patients in very high-risk categories and when certain medications may be contraindicated. Examples may include evaluation of pregnancy status and avoidance of pregnancy category X medications or avoidance of inappropriate anticoagulation in patients who have an epidural catheter in place. Many hospital pharmacists now have a mandate to automatically adjust certain medications for those patients with renal or liver dysfunction through an approved protocol, meaning that those patients can get correct dosing from time of order verification, rather than waiting for profile review.

Restricted Prescribing

For the most complicated, dangerous, or expensive drugs, it makes sense to restrict prescribing to physicians having sufficient familiarity, special training, or qualifications. Cancer chemotherapy is a one prime example. Requiring an infectious disease consultation for infrequently used, potentially dangerous, or high-cost antimicrobials (e.g., ganciclovir, liposomal amphotericin B, voriconazole) provides another. A final example (although there are many more) would be to restrict inhaled prostacyclin prescribing to critical care physicians experienced in treating acute respiratory distress syndrome (ARDS). Prescribing restrictions for cost control, however, should not impede the timely use of high-value therapies. Apart from ethical concerns, doing so might only reduce the acquisition cost for the drug, not saving money if outcome consequently worsens or length of stay is increased.

Eliminating Duplicate Therapy

A key step toward optimizing medication use is to eliminate duplicate or overlapping therapies. It is common to see patients prescribed suboptimal doses of two or more narcotics for pain or benzodiazepines for sedation. It is also common to see a patient with asthma or chronic obstructive pulmonary disease (COPD) have inhaled corticosteroids wastefully administered on top of high-dose parenteral or oral corticosteroids. Antibiotic therapy is frequently duplicated, sometimes with detrimental effects. For example, administration of a tetracycline with a penicillin will likely reduce the efficacy of the penicillin (because of its mechanism of action). Administration of azithromycin and levaquin together for community-acquired pneumonia may not be predictably deleterious, and it also has minimal additional antimicrobial benefit. In each case, a much better strategy is to reduce the number of drugs and to dose each to optimal effect. By doing so, fewer medications will be used, and as a result, cost, risk of adverse effects, and unwanted drug interactions will all decline.

Double Dipping

It is always a good idea to ask if one drug can be used to achieve two purposes. For example, in a patient with pneumonia and a urinary tract infection, is there one antibiotic or combination of antibiotics that can treat both conditions? Another example would be to select a benzodiazepine or propofol for sedation over another drug class in a patient who has had a seizure; choosing the benzodiazepine or propofol simultaneously provides a
“free” anticonvulsant. Likewise, using lactulose (vs. senna or milk of magnesia) in a patient with hepatic encephalopathy will provide laxative therapy while decreasing ammonia levels.

**Making Safer and Less Costly Choices**

In most cases, more than one appropriate drug alternative exists for treatment of any given condition. When two drugs are equally efficacious, it makes sense to choose the safer alternative with fewer known adverse effects or drug-drug interactions. One example would be opting to use fluconazole or voriconazole in place of amphotericin B to reduce the risk of renal injury. Similarly, many practitioners try to avoid aminoglycosides because of their potential for renal injury, even though they continue to be relatively inexpensive, often substituting a more costly antibiotic. In this case, the potential cost of renal injury will outweigh any benefit of the reduced medication cost. Sometimes, however, the safer alternative is the more inexpensive one (e.g., use of fluconazole vs. amphotericin B for certain fungal infections).

Drug-drug interactions should also be considered when two efficacious drug alternatives exist. Midazolam is a common sedative used in the ICU because of its relatively quick onset and short duration of action (especially helpful when trying to sedate while frequently assessing neurological status). However, because of its metabolism in the liver through the cytochrome system, it has over 800 known drug interactions, 42 of which are considered a major concern. If a patient is on multiple medications that interact with midazolam, it may make more sense to use propofol or dexmedetomidine (short acting, but more expensive) or lorazepam (longer acting, but similar cost). For each patient, the clinician must decide if the safety advantages between the two equally effective options justify the cost.

When two courses of therapy are equally safe and effective, cost should definitely be considered. For example, a urinary tract infection with *Escherichia coli* could be treated with generic enteral amoxicillin for pennies or with much more expensive (and broader coverage) intravenous extended spectrum penicillin for hundreds of dollars. Generic equivalents are almost always less expensive. Sometimes the choice is between two expensive drug therapies, as is the case with inhaled nitric oxide and nebulized prostacyclin for treatment of ARDS. Neither compound has proven outcome benefits, but both lower pulmonary artery pressures and may, at least temporarily, improve oxygenation in life-threatening hypoxemia. A protocol detailing who might qualify to receive these treatments and who has authority to prescribe them can save a large hospital hundreds of thousands of dollars annually with little compromise in treatment quality.

Establishing an automatic substitution program in which the least expensive therapeutically equivalent compound is substituted for a brand named medication also saves money. Hospitals may bundle medications together with a manufacturer to secure lower costs for all medications in that bundle. For example, the hospital may decided to buy a proton pump inhibitor, a cephalosporin antibiotic, and an antifungal together to get a better pricing on all three than they could get individually. This may mean that a hospital will specify a preferred proton pump inhibitor or histamine blocker on formulary for use in preventing stress ulcers. Often, patients are changed to the preferred agent on admission to lower costs to deliver hospital care. Other saving opportunities include allowing for automatic substitution of oral agents for intravenous agents when the gut works and bioavailability is favorable. For example, oral fluoroquinolones offer almost 100% bioavailability with significant cost savings over the parenteral route. The process of therapeutic substitution requires a proactive pharmacy committee and consensus, though not necessarily universal agreement, among local experts that the substitutions are reasonably equivalent. Reducing the number of like medications stocked by the pharmacy can also produce benefits. Pharmacy size is reduced, fewer personnel are necessary to track and manage inventory, and waste is reduced as fewer expired drugs are discarded. In the case of restriction or substitution, however, a multidisciplinary pharmacy committee must remain open to well-reasoned arguments for formulary additions or
exceptions, and a process for formulary waiver must exist for emergency situations.

**Modifying Frequency and Route of Administration**

Surprisingly, the cost of a course of therapy often depends more on the route and frequency of administration than the price of the drug acquisition cost. A patient is typically charged on average $20 to $40 for preparation of any intravenous medication. If the acquisition cost of that drug is $1, but is given four times a day, the preparation cost will far exceed the acquisition cost. In that situation, it may make more fiscal sense to choose an equivalent drug with higher acquisition cost that only needs to be given once daily. One example of this strategy is choosing ertapenem (given once daily) over piperacillin-tazobactam (given four times daily) for treatment of intra-abdominal infections. Even though ertapenem is more expensive to acquire, its overall daily cost is less. Other examples include substitution of once-daily tiotropium for ipratropium, which must be administered four times daily, or use of once daily low molecular weight heparin (LMWH) instead of unfractionated heparin (UFH) every 8 hours for venous thrombosis prophylaxis. Reducing the number of scheduled administrations each day also has been shown to be associated with fewer missed doses and thereby fewer treatment failures.

As already mentioned, the route of therapy can impact costs. In general, the cost of an equivalent dose of an oral medication is one tenth to one hundredth that of the same drug given intravenously. This vast discrepancy exists because intravenous preparations are usually more expensive to purchase, some drug is frequently wasted (in single-use only vials), and there are substantial labor costs associated with stocking, retrieving, mixing, transporting, and administering an intravenous preparation. Essentially, all patients eating or tolerating enteral nutrition can receive oral/enteral medications. In fact, many medications, including benzodiazepines, histamine blockers, proton pump inhibitors, narcotics, and some antibiotics, have equal bioavailability when given orally and intravenously. Hence, almost any time an intravenous preparation is changed to an oral route, substantial savings can be achieved.

Continuous infusion is the most costly method of administration because a dedicated line, infusion pump, specialized cassettes, and tubing (all of which are expensive) are required. Also, each infusion site increases the risk of infection, and the mere presence of an intravenous catheter in a patient with fever is likely to prompt an expensive evaluation as well as empiric antibiotics. Furthermore, if a central venous catheter must be inserted for access (e.g., for vasopressor therapy), the danger of infection persists and the risks of arterial puncture and pneumothorax are added. Sometimes switching from continuous infusion to intermittent intravenous dosing (e.g., benzodiazepines) or from continuous infusion to extended-duration infusion (e.g., antibiotics) may provide cost savings with additional benefits or at least minimized harm. Intermittent dosing of longer-acting agents can free up an intravenous line for administration of other required medications and blood products and in the process may avoid insertion of other catheters. Examples of this include using intermittent lorazepam (longer acting) in substitution of a continuous midazolam infusion or intermittent intravenous metoprolol (every 4 to 6 hours) in place of esmolol, which must be given as a continuous infusion.

The belief is often wrong that giving a medication by continuous infusion is mandated by the pharmacokinetics of the drug or confers more accurate control over its effects. Exact titration of a plasma drug level is rarely necessary or achievable, and drug levels often do not correlate with effects. Critically ill patients commonly have such altered pharmacodynamics that short-acting drugs can often have prolonged actions, many of which relate to the pH of the drug (basic vs. acidic) and whether it is hydrophilic versus lipophilic, both of which will be discussed later in this chapter. In addition, continuous infusions may obscure signs that the drug is no longer necessary. Continuously infused sedatives should undergo a daily reduction or holiday for this reason and doing so may help prevent ventilator-associated pneumonias.

**Drug Monitoring Costs**
A hidden cost of drug use is the coincident need to monitor drug levels and indices of organ function (e.g., serum creatinine for potentially nephrotoxic drugs, liver function tests for potentially hepatotoxic drugs, creatine kinase for daptomycin or platelets for linezolid). Although aminoglycosides and vancomycin are inexpensive to purchase, their costs are increased by the need for frequent peak and trough levels (currently, each vancomycin level costs in excess of $50), along with frequently monitored creatinine levels. Another example is the use of UFH versus LMWH for therapeutic anticoagulation. Although LMWHs carry a higher acquisition cost, because of ease of administration and lack of drug level monitoring, they often end up costing less overall. UFH, when being used for therapeutic anticoagulation, is usually given as a continuous infusion and is therefore associated with the need for an intravenous line and all of its associated problems and costs, as described previously. In addition, continuously infused UFH requires frequent monitoring of coagulation status, which implies costs of testing as well as associated nursing efforts to evaluate labs and make infusion adjustments.

**Avoiding Competing Therapies**

It makes no sense to provide one drug that negates or counteracts the effect of another. Yet, it happens frequently when pharmacists are not monitoring the medication profile. One example is the use of two agents that directly compete for the same substrates (e.g., use of nonsteroidal anti-inflammatory drugs [NSAIDs] and aspirin in acute myocardial infarction, or use of buprenorphine or other partial antagonists with opioids). One medication may also bind with another, making it less effective (e.g., simultaneous use of calcium carbonate antacids that chelate fluoroquinolone antibiotics). Finally, it is important to think about situations in which side effects of certain medications may counteract those of another (e.g., giving propofol, which is well known to cause hypotension, to a patient receiving a vasopressor). We often want to maintain or restart outpatient medications soon after admission, but careful thought must be given to whether or not it is appropriate to do so. It may be best, for example, to hold bupropion (which can lower seizure threshold) in a patient admitted for a traumatic brain hemorrhage or antihypertensive agents (e.g., ACE inhibitors or diuretics) in a patient admitted for septic shock on vasopressors.

**Optimizing Dosing**

One of the most important areas for safety improvement, which also often reduces drug cost, is careful attention to dosing as organ function changes. Most medications should be dosed less frequently or with smaller doses with renal and/or liver dysfunction.

Renal function can be assessed and tracked by serum creatinine, used in conjunction with equations that approximate creatinine clearance (most often using the Cockcroft-Gault equation). There are several good guides for dosing adjustments for almost any medication in renal dysfunction, but it is important to remember two vital things: first, serum creatinine usually lags behind actual declines in renal function by 1 to 3 days, and second, the calculated creatinine clearance is not valid until renal function plateaus. Therefore, it is advisable to follow trends in renal function, calculating an estimated creatinine clearance on a daily basis, and following urine output. A defensible strategy for adjusting drugs eliminated by the kidney is to assume that once the urine output is less than 0.5 mL/kg/h, the glomerular filtration rate is effectively zero. Just as there are times when doses must be reduced, occasionally drug requirements increase. Pregnancy and fully resuscitated major burn patients will have very high volumes of distribution and will likely require higher drug doses to have the same effect. Likewise, extensively traumatized and head-injured patients are often hypermetabolic in the first 2 weeks after injury and will, therefore, need more drug to accomplish the same effect during this period.

Dosing adjustments in liver dysfunction are more difficult (very few references exist on how to make them) because there is no in vivo surrogate (like serum creatinine for renal dysfunction) to predict their drug clearance. Patients at risk for impaired liver function include those who are malnourished or are on low-protein diets and
those patients who exhibit clinical signs of hepatotoxicity (nausea, vomiting, jaundice, hepatomegaly). Liver tests can also be helpful and are used to determine the level of liver dysfunction. These include serum bilirubin (levels above 4 to 5 mg/dL), prothrombin time (>1.5 times control), serum albumin (below 2.0 g/dL), and elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (usually three times the upper limit of normal). The reduction in clearance associated with liver disease can also be calculated by the Child-Pugh score, which assigns a score from 5 to 15 based on levels of encephalopathy, ascites, bilirubin, albumin, and prothrombin time. Using that score, patients are then categorized into Child-Pugh A (5 to 6 points, least severe liver disease), B (7 to 9 points, moderately severe liver disease), or C (10 to 15 points, most severe liver disease). Dose adjustments for drugs with a high hepatic extraction ratio can be made based on Child-Pugh scores if no drug studies are available. For patients in class A Child-Pugh, doses should be about 50% of normal, for patients in class B doses should be about 25% of normal, and for patients in class C it is generally recommended that a drug that is not affected by liver disease be used instead. Unfortunately, there are no convincing studies that affirm this dosing strategy. In general, drugs having a low hepatic extraction ratio are less problematic, because fluctuations in the unbound drug fraction will be rather small and will not significantly alter blood/plasma clearance of the drug. Dose adjustments for low hepatic ratio drugs should be aimed at maintaining normal total (i.e., bound plus unbound) plasma concentrations. “Pro”-drugs for which the metabolite is more biologically active (e.g., erythromycin, enalaprilat, codeine) should be avoided. Although there are limited data on dosing drugs in hepatic dysfunction, more information continues to surface on specific drugs and, if available, should be consulted.

Contrary to conventional wisdom, organ failure does not always mean thankless difficulty for pharmacotherapy. For example, many antibiotics have longer dosing intervals in renal dysfunction, thereby reducing cost and nursing time. Meropenem, for example, is normally dosed every 8 hours but is reduced to once daily in end-stage kidney disease. Another instance would be intentionally using a medication that is cleared by a failing organ to get a prolonged therapeutic effect (e.g., vancomycin in end-stage renal disease).

**Stopping Ineffective/Unnecessary Treatments**

Another method to improve safety while reducing costs is to eliminate ineffective prescribing habits. An example is provided by the use of dilute UFH to prevent clotting of most intravenous catheters. It is clear that this process is rarely necessary (saline works just as well), increases cost, and can lead to heparin-induced thrombocytopenia. Another example is repeated dosing of serotonin (5-HT) antagonists for nausea and vomiting. Even though 5-HT antagonists are effective when single doses are given to prevent postoperative nausea and vomiting, there are little data to suggest that redosing of these agents adds benefit.

Cost savings can also be achieved by addressing stop dates for medications. The most frequent example of this is seen with antibiotics. Broad-spectrum antibiotics should be tailored once culture data returns in order to reduce cost as well as prevent bacterial resistance. A classic example of this is stopping vancomycin or linezolid when there are no gram-positive bacteria on cultures. Stop dates on antibiotics should be placed when ordering antibiotics; almost every non-necrotizing pneumonia can be treated with 7 days of therapy (as long as the patient clinically improves early in therapy), and most intra-abdominal infections are now treated with 4 to 5 days of therapy. Placing appropriate stop dates at time of order entry will prevent continuation of antibiotic treatment for days or even weeks longer than what is needed.

Often, medication profile review reveals continuation of outpatient medications of questionable or no value during hospitalization. Most patients do not need vitamins or antihistamines, for example, during critical illness. It is generally recommended that oral hypoglycemic agents be held in critical illness (opting to use
insulin instead) because of fluctuating oral intake. Similarly, alpha-blockers (e.g., tamsulosin) can be held for those patients with urinary catheters in place. In general, at least initially, it is probably most appropriate to hold outpatient medications and reevaluate restarting them on a day-to-day basis.

**Shortening of ICU or Hospital Stay**

The choice of a more expensive drug may result in net cost savings by reducing the length of hospital stay. For patients needing therapeutic anticoagulation (e.g., for VTE or pulmonary embolism), LMWH or UFH are both options. LMWHs are generally more expensive, but because they may be given via subcutaneous injections in an outpatient setting (vs. intravenous UFH and oral warfarin), it may be the best cost saving option, and patients may be able to discharge days sooner. Another example is in choice of sedatives. Both propofol and dexmedetomidine are more expensive sedation options than either midazolam or lorazepam (both benzodiazepines). However, because propofol and dexmedetomidine are both shorter acting and may be more easily titrated off, they may lead to fewer ventilator and ICU days, thereby making them the more cost-effective choices.

**PHARMACOKINETICS**

Patients in the ICU are often given 10 or more medications simultaneously. As the number of medications, severity of illness, and patient age increase, so does the risk of an adverse drug reaction. Although few physicians have enthusiasm for studying pharmacokinetics (the sum of the processes the body is conducting on the drug, including absorption, distribution, metabolism, and excretion) or pharmacodynamics (the physiologic and biochemical effects of the drug on the body), understanding the basic concepts is essential to providing quality care. The critical care physician must develop a healthy respect for medications with narrow therapeutic margins and serious side effects. Intensivists must also learn how pharmacokinetics and pharmacodynamics differ between critically ill and ambulatory patients. Five major concepts are key to understanding appropriate drug dosing: absorption, distribution, and protein binding, metabolism, elimination, and half-life.

**Absorption**

Absorption is the ability of a drug to move from the site of administration into the bloodstream. The extent of absorption is typically measured in terms of bioavailability (the fraction of an administered dose that reaches systemic circulation). All drugs, other than those given by the intravenous route, are affected by absorption, but few studies have evaluated the affect that specific critical illnesses have on this process. Many factors may affect absorption including, gastric pH, gastrointestinal (GI) motility, bowel wall edema, splanchnic perfusion, first-pass metabolism, and enteral feeding interactions.

In states of decreased perfusion, the body's physiologic response is to shunt blood toward vital organs and away from the GI tract, which may decrease enteral absorption. In patients requiring vasopressor therapy, it is well documented that there are differing degrees of alterations in splanchnic perfusion. Bowel edema is a common cause of inefficient absorption.

There are many reasons for decreased gastric motility, including abdominal surgery, medications (e.g., opioids), ileus, immobility, traumatic brain injury, and electrolyte abnormalities (especially calcium or potassium). Absorption from the GI tract is favored when the drug is nonionized and lipophilic because absorption occurs by passive diffusion. The rate of absorption in the intestine will be greater than that in the stomach, even if the drug is predominately ionized in the intestine or largely non-ionized in the stomach. Any factor that accelerates gastric emptying such as right-sided positioning or use of motility agents (e.g., erythromycin, metoclopramide) will be likely to increase the rate of drug...
absorption, whereas any factor that delays gastric emptying is expected to have the opposite effect, regardless of the characteristics of the drug.

Enteral feeding may also affect drug absorption. Drugs given through an enteral feeding tube may adhere to the lumen of the tube (e.g., phenytoin, warfarin, amiodarone) or have incompatibilities with feeding tube formulations that limit bioavailability (e.g., fluoroquinolone antibiotics bind to cations in the tube feeds).

Given the physiologic shunting of blood to vital organs during shock, drugs may be slowly absorbed if given via the subcutaneous route. Common drugs used this way include insulin, UFH, and LMWH. Rates of absorption vary widely depending on the specific drug and local blood flow. In patients who are on vasopressor therapy or have more than a 10-kg fluid weight gain, the subcutaneous route should be considered less than normally reliable.

**Distribution and Protein Binding**

The distribution of a drug depends largely on two things: hydrophilicity and acid dissociation constant. During critical illness, changes in protein concentrations are known to occur that affect both the free (active) amount of drug available and the overall volume of distribution ($V_d$). Generally, decreased protein binding leads to increased free drug and overall increased $V_d$. Albumin concentrations are usually decreased during critical illness secondary to increased vascular permeability and decreased production and catabolism, thereby increasing the potential amount of free drug available. Hypoalbuminemia generally affects drugs that carry an acidic or neutral charge (e.g., amiodarone, midazolam, morphine, phenytoin, propofol) because these bind well to albumin. Conversely, alpha-1 glycoprotein concentrations increase during times of stress. This leads to lessened activity of drugs having basic charge (e.g., azithromycin, carvedilol, fentanyl, nicardipine, phenobarbital) because they are bound to alpha-1 glycoprotein.

Hydrophilic drugs (high-water solubility) have lower volumes of distribution than lipophilic (high-lipid solubility) drugs. Hydrophilic drugs (e.g., beta-lactams, vancomycin, aminoglycosides, morphine, hydromorphone) tend to distribute within the plasma volume and consequently depend on tissue perfusion for distribution. Therefore, in patients with poor perfusion secondary to shock (especially those on vasopressors) or disease state (peripheral vascular disease, diabetes), hydrophilic drugs will not distribute as well. In contrast, lipophilic drugs (e.g., azithromycin, fluoroquinolones, fentanyl, midazolam, propofol) have sufficient volumes of distribution to penetrate tissues, independent of perfusion. Therefore, lipophilic drugs are minimally affected by shifts in fluid (as may be seen in large-volume fluid resuscitation). Generally speaking, lipophilic drugs are minimally affected by changes encountered in critical illness.

**Metabolism**

The liver has a major role in the metabolism of many drugs, and critical illness, along with drug properties (extraction ratio and protein binding), can affect hepatic clearance. Hepatic drug elimination depends on blood flow, intrinsic clearance (the sum of all hepatic enzyme and transport activity involved in the removal of drug from the blood), and drug protein binding.

Hepatic blood flow is likely to be impaired during hypovolemia or cardiogenic/hemorrhagic shock. Mechanical ventilation may impede venous return and hepatic blood flow. Drugs with high extraction ratios (e.g., fentanyl, morphine, nitroglycerin, propofol) depend more on blood flow to the liver than on protein binding or enzyme function and will be most affected in these conditions. Conversely, metabolism of drugs with low extraction ratios (e.g., ceftriaxone, fluconazole, lorazepam, methadone and many others) depend less on hepatic blood flow and more on protein binding and enzyme function; these are significantly affected by moderate or severe liver failure or cirrhosis.
Elimination
Although the kidneys eliminate most drugs and their metabolites (through glomerular filtration and tubular secretion), drug elimination can also take place via the biliary tract, feces, and respiration. Dosing adjustments for drugs at steady state is calculated by estimating creatinine clearance (often using the Cockcroft-Gault or Jelliffe equations). When severe oliguria or anuria develops, however, it is difficult to assess true renal function.

Critical illness can lead to augmented renal clearance, especially in patients who are less than 55 years of age, after trauma, (particularly head trauma) or postoperative, have sepsis, are diagnosed with hematologic malignancies, or have significant burn injuries. Although there is no universally accepted definition of augmented renal clearance, a value of 10% above the upper limit of normal (GFR > 160 mL/min/1.73 m$^2$ in men and >150 mL/min/1.73 m$^2$ in women) has been proposed.

Optimal dosing of drugs in the acute kidney injury of critical illness is difficult because conclusive data are lacking. The Kidney Disease: Improving Global Outcomes (KDIGO) work group suggests that drug dosing be adjusted according to FDA-approved labeling. Even less is known about drug dosing in patients undergoing renal replacement therapy. In such cases, pharmacists should help specify appropriate schedules. Of course, when available, protocols based on fluctuations in renal function may also assist in dosing adjustments.

Half-life
After administration, most drugs exhibit a two-phase concentration profile corresponding to initial distribution and then elimination. The serum half-life ($t_{1/2}$) is the time required for initial drug concentration to fall by 50% without further supplementation. The $t_{1/2}$ incorporates distribution and clearance effects to give a useful index for predicting the time required to achieve steady state (usually 5 half-lives) and to determine the dosing interval. With repeated intermittent dosing, most drugs accumulate and wash out exponentially to their final concentrations (first-order kinetics). Drug monitoring before steady state will underestimate the eventual peak, and trough concentrations and should, therefore, be avoided (Fig. 15-1). Unfortunately, the stated half-life of drugs typically is determined in healthy individuals and rarely accurately reflects the kinetics of a compound in the critically ill. Commonly, long-term dosing and dysfunction of several organ systems prolongs half-life. For example, drugs that rely on renal elimination may have a prolonged functional half-life in patients with renal dysfunction (e.g., active metabolites of midazolam, carbapenem antibiotics), and similarly, drugs that rely on metabolism by the liver (e.g., propofol, argatroban) may have prolonged effects in patients with hepatic dysfunction.
FIGURE 15-1. Dosing and elimination kinetics. After a single dose, drug concentration falls exponentially to undetectable levels over approximately five half-lives (dashed line). During continuous infusion or intermittent administration of smaller maintenance doses (without load), a steady-state concentration is not achieved until five half-lives have elapsed (solid line). The therapeutic range can be achieved and maintained quickly by combining a large initial loading dose with a maintenance schedule of either type.

ROUTES OF ADMINISTRATION

Goals of Drug Administration
The aim of drug therapy is to rapidly achieve and maintain effective, nontoxic tissue drug concentrations. In critically ill patients, these goals are frequently met by combining appropriate loading doses followed by maintenance regimens. During intermittent dosing, drug levels may demonstrate peaks and troughs that potentially expose patients to toxic or subtherapeutic levels. In an attempt to avoid these fluctuations, many drugs in the ICU are given as a continuous or titratable infusion (vasopressors, sedatives, analgesics). Other drugs (especially antibiotics) may avoid these fluctuations in peak and trough levels and achieve goal therapeutic ranges by extended infusion. Instead of infusing in over 1 hour, they may be infused over 8 hours. Highly lipid-soluble drugs, drugs with long half-lives, and those with a large volume of distribution may progressively accumulate for long periods of time before toxic side effects emerge. Deterioration of renal or hepatic function may impair drug excretion. The addition of new drugs to an established regimen may also alter metabolism, compete for protein binding or alter absorption.

Inhalation
Use of inhaled drugs offers the advantage of rapid absorption across a rather large surface area with minimal adverse effects. Targeting the drug to the target organ generally allows for a lower dose than is needed with systemic delivery, with fewer and less severe adverse effects. There are distinct disadvantages to this delivery method, however, including need for ancillary equipment (e.g., spacer), inconsistent dosing technique, low efficiency of lung deposition, contamination of ambient air, and loss of drug.
There are three types of devices to deliver aerosolized drugs, and all can be clinically effective if used correctly; these include the metered-dose inhaler (MDI), the dry powder inhaler (DPI), and nebulizer. Although lung deposition efficacy has increased with newer-generation devices, it remains in the 40% to 50% range.

Use of inhaled drugs in the ICU is appealing to reduce the number of drugs given parenterally, but this method of drug delivery is complicated by deposition of the aerosol particles in the ventilator circuit and the endotracheal tube. Both inhaled beta-adrenergic (albuterol) and anticholinergic (ipratropium) agents have proven efficacy in mechanically ventilated patients. Efficacy of drug delivery depends on several factors, including type of nebulizer used, proximity to the airway opening, actuation of an MDI into an in-line chamber spacer, midinspiratory timing of MDI actuation, ventilator mode, tidal volume, circuit humidification, and ventilator duty cycle. With proper technique, it has been shown that four (4) puffs of an MDI will produce significant and near-maximal therapeutic effects that are comparable to those obtained with 6 to 12 times the same dose given by a nebulizer. Apart from its labor saving, quicker delivery and lower cost advantages, many practitioners consider MDIs more efficacious to prescribe during mechanical ventilation.

Endotracheal Instillation
The endotracheal route of administration utilizes the absorptive capacity of the lung. A drug solution is introduced through the endotracheal tube and allowed to migrate into the lower respiratory tree. Delivery to the distal site of absorption is facilitated by insufflation using a manual ventilator (or similar device such as an artificial manual breathing unit). The proposed site of circulatory absorption is the alveolar capillary circulation. Only certain drugs are safe and effective when given this way.

There are several considerations when using the endotracheal route of drug administration. First, the proper technique must be employed. Patients must be tilted (avoid a fully upright position) to allow the drug to filter into the lower respiratory tree. Adequate ventilation also plays an important role in distribution. Most reports suggest manual ventilation at least 5 to 10 times afterward to assure maximal distribution. Drugs should be diluted in 0.25 mL (for pediatric patients) to 10 mL (for adults) of 0.9% saline or sterile water. Somewhat arbitrary recommendations for endotracheal dosing are 2 to 3 times the usual intravenous doses for nearly all candidate drugs.

Endotracheal drug administration has typically been reserved for cardiopulmonary resuscitation in which no intravenous access is available. Drugs typically given in this situation can be remembered by the mnemonic NAVAL (naloxone, atropine, vasopressin, epinephrine, and lidocaine). Epinephrine, atropine, and naloxone are reported to be effective and appear to have no added adverse effects when given via the endotracheal route. There are risks with other drugs, however. Sodium bicarbonate may inactivate lung surfactant, isoproterenol and calcium chloride are reported to cause tissue necrosis, and bretylium is poorly absorbed and does not result in adequate blood levels. When the more reliable intraosseous (IO) access can be quickly attained and immediately accomplished, endotracheal dosing is seldom used (see below).

Intraosseous (IO)
Intraosseous infusion is a rapid and safe method for obtaining parenteral access in patients with difficult venous access. Infusion of fluids and drugs into the bone marrow space has been researched since the 1920s, and it has since been verified that fluids and drugs administered through the IO space reach the central circulation as quickly as those given via a central venous catheter and faster than those given via a peripheral catheter. Mean IO pressures are close to the mean systemic pressure—much closer to central venous than to arterial values. IO can also be used for drawing blood samples. Although sometimes used when establishing urgent venous access proves difficult, the most frequent clinical situations in which IO is utilized remain cardiopulmonary resuscitation
A wide variety of drugs are delivered safely through IO access including adenosine, amiodarone, atropine, epinephrine, insulin, morphine, propofol, and many others. Theoretically, any medication that can be given intravenously can be given via IO access. Each drug should be flushed with 10 mL of fluid to keep it from dwelling in the medullary cavity.

In the arrest setting, blood concentrations of drugs will vary by IO injection site. For instance, peak blood concentrations are achieved faster for sternal IO than for tibial IO. In addition to slower peak concentrations, the peak concentration achieved by the tibial route may be only two thirds of that delivered via the sternum. Sternal IO time to peak blood concentrations and total delivered dose appear similar to central venous administration. Risks to using the IO route include osteomyelitis, bacteremia, soft tissue infection, and extravasation.

**Intravenous Injection**

The intravenous (IV) route is the most reliable route of drug administration and avoids problems of bioavailability and delays associated with absorption. Unfortunately, the IV route can result in dangerously high peak drug concentrations, especially when a drug is infused rapidly through a central venous catheter. Cardiac toxicity can occur with phenytoin (hypotension) or potassium (dysrhythmias) during rapid IV infusions of these medications. IV infusions allow the administration of drugs that would otherwise be too caustic, unstable, or poorly absorbed to dose via other routes. At steady state, continuous infusions will sustain drug levels, limit peaks and troughs, and avoid the associated problems of subtherapeutic levels and toxicity. It must be kept in mind, however, that if the patient develops renal or hepatic dysfunction, continuous infusion rates should be adjusted to avoid excessive drug accumulation.

Continuous IV infusion is the most costly method of drug administration and often is not necessary. For example, intermittent dosing of pain medications and sedatives is often just as effective and often shortens ICU length of stay. High costs arise from two sources: IV drugs are typically the most expensive formulations and substantial costs are also incurred in securing and maintaining IV access. The incremental costs of inserting an IV line are often overlooked and are increased even more if complications (e.g., hemothorax, pneumothorax, or catheter-related sepsis) occur. IV dosing can be avoided for many medications that achieve similar blood concentrations when given orally. Bioavailability for some orally given medications approaches 100% (e.g., fluoroquinolones, fluconazole, metronidazole).

**Subcutaneous Injections**

Subcutaneous (SQ) injections may be appropriate if the drug is non-irritating and administered in a small volume (approx. 1 mL or less). Advantages of SQ administration include relatively rapid onset in nonshock states, reasonably uniform absorption (in normal patients), and avoidance of first-pass metabolism. Disadvantages of SQ administration include localized pain, abscess formation, infection, expensive cost, nerve damage, and local hematomas. Typical drugs that are given via this route in the ICU include insulin and anticoagulants (e.g., UFH and LMWHs).

Critical illness can affect SQ absorption, making this route of administration less desirable in this population. During circulatory shock, blood is shunted to vital organs, depriving the subcutaneous tissue of normal perfusion. One study evaluating the use of enoxaparin in patients receiving vasopressors found that the anti-factor Xa levels were significantly lower and not within the recommended therapeutic range. Profound edema (>10 kg of fluid weight gain) also impedes absorption. Morbid obesity may also make true SQ injection a challenge. Therefore, close monitoring of medications being given via SQ administration is recommended or its use should be avoided.
**Intra-arterial Injections**

Intra-arterial injections are used to provide localized effects of a drug to a particular organ. Advantages of this type of administration include providing the highest concentrations of drug locally with maximum effect, minimizing systemic toxicity, and avoiding first-pass metabolism of the liver and the lung. The main disadvantage is that this type of administration requires great care and skill and therefore must be done by experts.

There are several examples of intra-arterial drug administration. Cerebral vasospasm is commonly seen following aneurysmal subarachnoid hemorrhage but may also follow other intracranial hemorrhages (e.g., intraventricular or arteriovenous malformation hemorrhages). Intra-arterial injection of several drugs (e.g., nimodipine, papaverine, nicardipine, milrinone, verapamil) may be helpful in treating cerebral vasospasm by dilating the spastic artery. Although this type of therapy has been shown to help improve vasospasm, it is relatively short-lived and will require repeated therapy when vasospasm returns.

Other examples of successful intra-arterial administration include chemotherapeutic agents for retinoblastoma, hepatocellular carcinoma, and CNS tumors, as well as thrombolytic therapy in peripheral artery disease, ischemic stroke, and very rarely, in massive pulmonary embolism occurring in high-risk patients.

**Intrathecal Therapy**

Intrathecal drug delivery involves direct injection of the drug into the cerebral spinal fluid (CSF) within the intrathecal space of the spinal column. This allows for circumvention of the blood-brain barrier and therefore allows delivery of smaller drug doses with reduced systemic side effects.

Intrathecal drug delivery is used in chronic spasticity from conditions such as multiple sclerosis and cerebral palsy (e.g., intrathecal baclofen), management of cancer, chronic nonmalignant or neuropathic pain (e.g., intrathecal morphine), chemotherapy treatment for lymphomatous meningitis (e.g., methotrexate, cytarabine), and antibiotic treatment adjuvant to systemic antibiotic therapy in bacterial meningitis/ventriculitis and other infections of the central nervous system (e.g., gentamicin, vancomycin).

Intrathecal formulations are sterile isotonic drug solutions. The volume of intrathecal injections ranges from 0.5 to 5 mL. Achieving drug solubility in such a small volume can be a challenge for lipophilic agents. It is imperative that intrathecal formulations are free from microorganisms because CSF protein and glucose can be an ideal environment for bacterial growth; therefore, these formulations must be prepared using aseptic techniques. Also, intrathecal formulations must be preservative-free, because studies have shown that preservatives such as parabens and benzyl alcohol can cause inflammation of the arachnoid membrane and risk nerve damage.

**Intraperitoneal Therapy**

The membranes of the peritoneal cavity can exchange drugs and metabolites as during peritoneal dialysis in end-stage renal disease patients. Transport of drugs across the peritoneum is affected by dosing variables (e.g., dose, volume, temperature, duration, composition of carrier solution), drug properties (e.g., molecular weight, ionic charge, lipid/water solubility), and characteristics of the peritoneum (e.g., surface area, charge, permeability).

Intraperitoneal (IP) antibiotics are commonly used to treat episodes of bacterial peritonitis in peritoneal dialysis patients. Using the IP route avoids the systemic IV route and targets the involved tissue directly. Commonly, cefazolin or vancomycin is used for empiric gram-positive bacterial coverage, and ceftazidime or gentamicin is used for gram-negative bacterial coverage. There are many published antibiotic treatment regimens for treatment of peritoneal dialysis-associated peritonitis, and the International Society for Peritoneal Dialysis (ISPD) periodically updates the guideline as new information becomes available. Note that chemical peritonitis has been reported with high doses of vancomycin, and only short courses of aminoglycosides are recommended to avoid
loss of residual renal function. Some agents intended for transfer into the general bloodstream can be given via the IP route. These include insulin, heparin, erythropoietin, nutrition, and gene therapy.

**Transcutaneous/Transdermal Administration (Patches)**

Cutaneous drug absorption depends on skin permeability, temperature, blood flow, moisture content, and the presence of dermatologic disorders. There are many drugs available in a patch formulation, including nitroglycerin, clonidine, fentanyl, scopolamine, lidocaine, and many others. Patches are a great option in stable patients who are unable to take enteral formulations or may want the convenience of prolonged dosing (some patches are changed on a weekly basis). In the ICU setting, however, patches tend to be problematic for several reasons. First, as stated above, drug release from a patch is regulated by temperature, so if the patient has an elevated temperature, the drug will be more rapidly released from the patch, potentially resulting in toxic levels. Second, the patch takes time to start working after placement (anywhere from 6 to 18 hours depending on the drug in the patch because of diffusion through the skin), and therefore, once the patch is removed, it will take about that same amount of time for the drug effect to stop working. This could be problematic if you have placed a clonidine patch, for example, and your patient becomes hypotensive.

**Intraocular Drugs**

Although ophthalmic preparations (e.g., drops, ointments, suspensions, emulsions) may contain a very small amount of drug, it should be remembered that these medications can still have significant systemic side effects. When administered, eyedrops come into contact with the conjunctiva and the secretory membranes of the tear canals, eventually reaching the circulatory system through the mucosa of the nose and throat. Atropine eyedrops, which are administered to achieve mydriasis for retinal examination, may cause fever, headache, facial erythema, dry mouth, high blood pressure, difficulty in concentration, cramps, and blurred vision. Glaucoma medications, like ophthalmic beta-blockers, may cause bradycardia, reduced blood pressure, dry eye, and exacerbate asthma and congestive heart failure. Therefore, any drug given via the ophthalmic route should be reviewed for its potential side effects and monitored by both the patient and physician.

**Enteral Administration**

Bioavailability of enterally administered drugs can be limited by gastric pH, bowel wall edema, enteral feeding interactions, and first-pass metabolism. Effective enteral therapy requires gut motility, mucosal perfusion, and epithelial integrity. Patients with ileus, gut hypoperfusion, or atrophic or injured epithelium are poor candidates for enteral therapy because absorption will be limited. Drugs given in aqueous solutions are more rapidly absorbed than those given in oily solutions, and nonionized drugs are more readily absorbed than ionized drugs. A few poorly absorbed drugs (e.g., vancomycin, polymyxin) are intentionally given enterally to act selectively in the gut. Drugs destroyed by an acidic pH may be partially protected by enveloping them with an enteric coating. Conversely, other drugs require acid for activation or absorption (e.g., sucralfate, ketoconazole, iron), a point that deserves consideration in patients receiving acid-suppressive therapy.

Liquid preparations are the preferred formulations when possible because they are readily absorbed and are less likely to clog feeding tubes. Elixirs and suspensions are preferred over syrups because syrups tend to cause more clumping when exposed to enteral feedings. Many liquid preparations are extremely hyperosmolar or contain large amounts of sorbitol, increasing the risk of GI intolerance. Suspensions generally contain less sorbitol, and even though they still have high osmolality, diluting them with water will help decrease tonicity and thereby make them a more desirable formulation.
Some formulations are not appropriate for enteral administration. These include lansoprazole oral suspension granules and mineral oil (which are too viscous and may occlude the feeding tube), sucralfate suspension (may cause an insoluble mass or bezoar formation), and extended, sustained, or delayed-release formulations (listed below). Although solid dosage forms (e.g., tablets, capsules) can be used, the tablets should be crushed and the capsules should be opened and the contents mixed with 15 to 30 mL of water before delivery.

It is important to note that many sustained or delayed-release drug formulations (e.g., any drug that has ER, DR, SR, XL after its name) should not be crushed and given via the enteral route. It is often best to use the immediate release of these formulations and divide them appropriately throughout the day when using the enteral route. For example, if the patient was taking metoprolol succinate 50 mg daily, it would be more appropriate to use metoprolol tartrate 25 mg twice daily if given via the enteral route. If there is any doubt whether or not a medication can be crushed and given via an enteral route, it is best to either consult a “do not crush” list or your clinical pharmacist.

Although interactions between medications and nutrients have been appreciated for years, specific recommendations on how to administer the majority of medications to patients receiving continuous enteral nutrition are lacking. If possible, either a nutritionist or pharmacist should be reviewing appropriateness of medications for enteral administration.

**Sublingual/Buccal Administration**

When enteral drugs cannot be given or are contra-indicated, sublingual or buccal administration may be an option. Only minute quantities of drug are absorbed across intact oral epithelium; therefore, an effective sublingual/buccal drug must be potent and lipid soluble. These methods of administration offer the advantages of quick absorption and avoidance of first-pass metabolism but are disadvantageous because they may irritate the oral mucosa, can only be given in small quantities or in an expensive oral disintegrating tablet, and only constitute a small percentage of drugs.

Nitroglycerin is probably the most common sublingual formulation given. If swallowed and absorbed enterally, nitroglycerin is rapidly eliminated by first-pass metabolism, but because drugs absorbed from the sublingual space drain directly to the superior vena cava, such first-pass metabolism is bypassed, increasing bioavailability. Another example of a sublingual formulation is atropine, which is often given to help handle secretions when patients are transitioned to end-of-life care. Although scopolamine patches may also be given for this indication, atropine is often more desirable because of the more rapid onset. Risperidone, olanzapine, and other selected drugs with useful ICU applications may occasionally be available for delivery in this fashion.

**Rectal Administration**

Rectal administration of certain drugs can occasionally be useful in children, combative patients, patients with problematic venous access, refractory vomiting, and ileus. Hepatic first-pass metabolism is less extensive with rectally administered drugs than with orally administered ones, but it is still significant. Unfortunately, rectal administration sometimes results in erratic and incomplete absorption and therefore is less desirable than either oral or parenteral dosing. Rectal dosing is best confined to sedatives (e.g., diazepam for seizures), antiemetics (e.g., promethazine), antipyretics (e.g., acetaminophen), and laxatives (e.g., glycerin).

**SUGGESTED READINGS**


Chapter 16
Nutritional Support and Therapy

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Co-written with

• Key Points

1. Consequences of malnutrition that affect patient outcomes include poor wound healing, compromised immune status, longer hospital length of stay, and increased mortality.

2. It is important to assess a patient's nutritional risk upon admission to the ICU and specify goals of nutrition therapy.

3. Feeding is ideally started within the first 24 to 48 hours following onset of critical illness, given its nutritive and nonnutritive benefits.

4. Enteral nutrition is always preferred over parenteral nutrition in the critically ill patient with a functioning GI tract.

5. Close monitoring of patients receiving enteral and parenteral nutrition therapy is an important part of preventing and treating complications.

There is growing evidence about the importance of appropriate nutrition in the critically ill patient. In the past, nutritional support in the critically ill was simply thought to provide exogenous fuel to preserve lean body mass and support the patient through the stress response. It is now known that providing enteral nutrition (EN) also helps to maintain gut integrity, modulate stress and the systemic immune response, and reduce disease severity. Nutrition-based therapies also offer an opportunity to protect or establish a beneficial gut microbiome. As severity of illness worsens and drug therapy, particularly antibiotics, is applied, the diversity and composition of gut bacteria declines with introduction of pathogenic bacteria which may contribute to nosocomial infections, sepsis, and organ failure (Fig. 16-1). In fact, achieving early EN support within the first 24 to 48 hours of admission has been associated with decreased infectious morbidity and reduced ICU length of stay. Although research has strengthened our understanding of the field, nutritional support of the critically ill remains a science in evolution. Unlike other areas of medicine, there is no definitive imaging study or lab value to diagnose malnutrition.

THE METABOLIC RESPONSE TO STRESS IN CRITICALLY ILL PATIENTS

The metabolic alterations that occur in a stressed state resulting from illness, injury, or infection are quite different from the metabolic changes that result from simple starvation. During simple starvation, the body aims to conserve energy and preserve protein stores. Metabolism is decreased, and body fat is preferentially used for energy. During the stressed state of illness, metabolism increases as a result of a series of changes in counterregulatory hormones, prostaglandins, and cytokines. Adjustments are made to mobilize energy by releasing glucagon, which aids in glycogenolysis (breakdown of glycogen to glucose) and gluconeogenesis (production of glucose from amino acids and other noncarbohydrate substrates). Protein catabolism and synthesis increase as protein is utilized to repair damaged tissue and manufacture inflammatory mediators such as C-reactive protein. Hyperglycemia and protracted wasting of lean body mass result. If the illness or injury sustained, protein-calorie malnutrition becomes inevitable.

MALNUTRITION IN THE ICU
Malnutrition can result from inadequate intake, increased metabolic requirements, impaired absorption, altered transport of nutrients, and ineffective nutrient utilization. It is estimated that at least one third of patients arrive at the hospital already malnourished. If nutritional condition goes untreated, many of those patients continue to decline. Even in patients who are not malnourished upon admission, one third will become malnourished while in the hospital. It is not difficult to understand how this might occur. Aside from the malnutrition that develops as a result of a prolonged inflammatory state, there are also issues that prevent normal oral intake including prolonged intubation, frequent nothing by mouth (NPO) status for diagnostic or therapeutic procedures, and GI complications or symptoms that limit enteral intake. Even if a patient is able to tolerate an oral diet, intake is often reduced because of poor appetite that accompanies illness.

FIGURE 16-1. As severity of illness worsens and drug therapy is applied, the diversity and composition of the gut microbiome in health decline. Opportunistic pathogens tend to fill the microbiologic void.

Malnutrition is associated with poor wound healing, compromised immune status, impaired organ function, muscle wasting, and increased mortality risk. Even a 10% loss of lean body mass has been associated with immune suppression and increased risk of infection. Malnutrition predisposes to longer hospital length of stay, higher readmission rates, and higher treatment costs.

There is no single laboratory measure that can diagnose malnutrition. Traditional serum protein markers (albumin, prealbumin, transferrin, and retinol-binding protein) quickly become altered in the acute-phase response of critical illness and inflammation. The serum levels of these proteins decrease, promoting edema formation. Reprioritization of hepatic protein synthesis during illness makes traditional protein markers poor indicators of nutritional status, especially in the ICU setting. Clinicians have been encouraged to use a list of characteristics to evaluate nutritional health. Two or more of the following establish the diagnosis: insufficient energy intake, weight loss, loss of muscle mass, reduced subcutaneous fat, localized or generalized fluid accumulation (that can mask weight loss), and diminished functional status (Table. 16-1).

NUTRITION ASSESSMENT AND CANDIDATE SELECTION FOR NUTRITION SUPPORT
It is important to determine a patient's nutritional risk early in the hospitalization. Nutritional risk can be determined by validated screening and assessment instruments, such as the Malnutrition Screening Tool. Historical data regarding weight and recent dietary intake, anthropometric data, and a physical examination-focused nutritional assessment are all part of a full nutritional assessment. Along with nutrition risk, a patient's disease type and severity should also be taken into consideration.

Patients at high nutritional risk upon ICU admission or those with severe disease should be considered for early EN support if intake from oral diet is certain to prove inadequate. Although patients at high risk are most likely to benefit from initiation of enteral support within the first 24 to 48 hours of admission, all critically ill patients requiring mechanical ventilation are appropriate candidates, because of the nonnutritive benefits.

If EN is not feasible because of compromised GI function, then decisions about when to start PN support depend more heavily on the patient's nutritional status prior to ICU admission. If the patient is at low nutrition risk (was meeting their nutritional needs just prior to admission), then PN should be withheld over the first 7 days of the ICU course. This recommendation was made after thorough literature review from representatives of the American Society for Parenteral and Enteral Nutrition (ASPEN) and Society of Critical Care Medicine (SCCM) and released in a published guideline statement in 2016. The risk/benefit ratio for use of PN in the ICU setting is much greater than for enteral feeding, because PN carries with it heightened risk for infectious complications. Of course, if a patient has a diagnosis that makes them dependent on PN (e.g., short bowel), then PN should be continued through the patient's ICU stay if safe to do so.

When a patient is at high nutritional risk or is severely malnourished upon their ICU admission and EN is not possible, then the recommendation is to start PN as soon as feasible. Studies that look specifically at the malnourished ICU patient population show that withholding nutrition is associated with higher risk of mortality and higher rates of infection than encountered when PN is provided.

### Table 16-1. Malnutrition Defined
Refeeding Syndrome

When assessing a patient's nutritional status and initiating nutrition support therapy, one factor to consider is risk for refeeding syndrome. Refeeding syndrome occurs when a starved or malnourished patient first begins receiving generous nutritional support, particularly in the form of carbohydrate. This triggers rapid fluid and electrolyte shifts and stimulates insulin secretion that in turn decreases distal renal tubular excretion of sodium and water. Hyperinsulinemia also promotes the intracellular migration of phosphorus, potassium, and magnesium, occasionally resulting in profound disturbances of muscular function and cardiac conduction. Signs of refeeding syndrome include hypophosphatemia, hypokalemia, and hypomagnesemia, along with edema. Symptoms of this syndrome may include generalized fatigue, lethargy, muscle weakness, and cardiac arrhythmias.

To prevent refeeding syndrome, EN or PN should be started slowly in severely malnourished patients and in those who have been NPO for a prolonged period of time. Initiating nutrition support at 15 to 20 kcal/kg/day or at basal calorie levels is considered acceptable. This syndrome can also occur in patients resuscitated with IV solutions containing dextrose. As nutrition support (or IV dextrose) is initiated, electrolytes should be monitored daily over the first few days of feeding or until stable and replaced as needed. Short-term thiamine supplementation may also be considered. Within 2 to 3 days, or once risk of refeeding syndrome is minimized, the level of nutrition support can be increased to better meet the patient's full estimated needs.

NUTRITIONAL REQUIREMENTS

Energy/Calories

The gold standard for determining energy requirements in critically ill patients is provided by indirect calorimetry. Indirect calorimetry involves using a metabolic cart to measure a patient's resting metabolic rate. Resting energy expenditure (REE) is determined using the abbreviated Weir equation (see following) by measuring oxygen
consumption (\(\text{VO}_2\)) and carbon dioxide production (\(\text{VCO}_2\)). However, many hospitals do not have access to this costly equipment and lack sufficient clinical staff/expertise to perform the test and interpret the results. Accuracy of REE determinations depends on proper setup and calibration of the measuring device, as well as achieving a “steady state”—often difficult in the critically ill.

**FIGURE 16-2. Caloric requirements in stress.**

(Units of \(\text{VO}_2\) and \(\text{VCO}_2\) and REE are L/min kcal/day.)

When indirect calorimetry is not available to determine energy requirements, a published predictive energy equation or weight-based equation (25 to 30 kcal/kg/day in the nonobese patient) should be used. There is significant variation in the accuracy of predictive equations, owing to weighting of their factors affecting energy expenditure, such as weight, body composition, degree of inflammation, treatments, and body temperature. Predictive equations are less accurate in the underweight and overweight patient populations. When estimating needs, a clinician should also take into account the phase of metabolic response for the patient’s disease process and the presence of wounds or increased energy needs for healing. **Figure 16-2** delineates conditions for which caloric needs are often heightened. Even though caloric needs shown in this figure are quite elevated, we do not always provide patients their full estimated needs, especially during the first week of critical illness when overfeeding should be avoided. Energy intake from sources other than nutrition support should also be considered, such as calories provided from dextrose-containing IVFs or lipid-rich propofol infusions.

The catabolic phase of illness that follows resuscitation typically usually lasts 7 to 10 days and involves fever, hypercatabolism, and increased oxygen demands. The goal of nutrition support during this period should be
adequate protein intake with avoidance of overfeeding. Excess calories can exacerbate respiratory failure by increasing carbon dioxide production and minute ventilation requirement. In fact, in the critically ill obese patient population with body mass index (BMI) greater than 30, nutrition experts now recommend high-protein hypocaloric feeding to preserve lean body mass while minimizing the metabolic complications of overfeeding.

The anabolic stage that follows the catabolic phase of illness is characterized by need to replete lean body mass and adipose tissue. During this period, caloric delivery may be increased and underfeeding should be avoided. Underfeeding for greater than 10 to 14 days can lead to deterioration of lean body mass, immunosuppression, increased risk of infections, and poor wound healing.

**Protein**

Healthy normal adults require approximately 0.8 g/kg/day of protein; however, the average ICU patient may need double that amount—up to 1.5 to 2.0 g/kg/day (Fig. 16-3). The corresponding amount of nitrogen supplied may be calculated by dividing grams of protein by 6.25. Recent studies in critical illness suggest that the dose of protein needed in critically ill patients is higher than previously thought. Research has demonstrated that adequate intake of protein (more strikingly than adequate energy intake) leads to better outcomes (e.g., decreased mortality). However, providing protein in amounts greater than the body requires is not beneficial, as amino acids cannot be stored and overfeeding can result in azotemia. It is difficult to estimate protein requirements in the ICU, but the patient's overall condition and sources of protein loss should be considered. In severe sepsis, multitrauma, or burn injury, protein turnover is usually very high. Protein needs increase whenever there are losses via surgical drains, chest tubes, open abdomen, or large wounds or when patients require intermittent hemodialysis or continuous renal replacement therapy.

![FIGURE 16-3. Protein requirements in stress.](image)

The adequacy of protein delivery can be assessed using a urinary nitrogen balance study; however, in practice, such studies are laborious, expensive, and uncommonly performed. The calculation of urinary nitrogen balance is based on several assumptions, including urea accounting for 80% of total urinary nitrogen loss. Nonurinary
(normally, skin and stool) losses of nitrogen are thought to be fairly small (approx. 2 g/day), unless there are other sources of loss, such as through fistulas or open surgical wounds. It should be noted that acute illness promotes urinary excretion of nitrogen as a result of catabolism, and it may be difficult to achieve a positive nitrogen balance in this setting. The balance between nitrogen intake and loss can be approximated using this formula:

\[
N_2 \text{ balance} = \left( \frac{\text{protein intake}}{6.25} \right) - \left( \left[ \text{UUN} + 20\% \text{ of urinary urea losses} \right] + \text{non-urinary losses} \right)
\]

**Lipids**

Lipids provide a rich source of calories in a relatively small volume. Some lipid intake is required to prevent the occurrence (over several weeks) of essential fatty acid deficiency. It is estimated that as little as 2% to 4% of total calorie intake from linoleic acid and 0.25% to 0.5% of total calories from α-linolenic acid are enough to prevent essential fatty acid deficiency in patients receiving specialized nutrition support. Most enteral formulas provide adequate lipid in their formulations to meet this requirement, and the use of IV fat emulsions at least one to three times a week (depending on the lipid volume and formulation) in patients receiving PN will prevent deficiency. Another source of lipid calories in the critically ill population is the intravenous sedating drug propofol, which uses lipid as its vehicle for infusion. Although less concentrated than nutritional lipid supplements intended for the purpose, the lipid provided by this medication provides 1 to 2 kcal/mL of drug infused and must be considered.

<table>
<thead>
<tr>
<th>Vitamin Deficiency</th>
<th>Clinical Syndrome/Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Decreased vision, dermatitis, impaired wound healing</td>
</tr>
<tr>
<td>B₁ (thiamine)</td>
<td>Peripheral neuropathy, Wernicke-Korsakoff syndrome</td>
</tr>
<tr>
<td>B₂ (riboflavin)</td>
<td>Glossitis, cheilosis, pruritus</td>
</tr>
<tr>
<td>B₃ (niacin)</td>
<td>Pellagra (dermatitis, diarrhea, dementia)</td>
</tr>
<tr>
<td>B₆ (pyridoxine)</td>
<td>Dermatitis, cheilosis, calcium oxalate urinary stones</td>
</tr>
<tr>
<td>B₁₂ (cyanocobalamin)</td>
<td>Pernicious macrocytic anemia, cognitive decline</td>
</tr>
<tr>
<td>Biotin</td>
<td>Alopecia, myalgias, paresthesias, dermatitis</td>
</tr>
<tr>
<td>C</td>
<td>Scurvy (anemia, hemorrhage, gum swelling, muscle weakness), poor wound healing</td>
</tr>
<tr>
<td>D</td>
<td>Osteomalacia, osteoporosis</td>
</tr>
</tbody>
</table>
Vitamins and Trace Elements

Vitamins and trace elements serve as antioxidants and play key roles as intracellular cofactors for enzymatic and energy-generating reactions. More than a dozen different vitamins and trace minerals have been identified as essential for normal physiologic function. It is well recognized that levels of these substances are often abnormal in the plasma of critically ill patients.

Fat-soluble vitamins (A, D, E, K) are less prone to acute changes induced by critical illness by virtue of their relatively large storage pool in most patients. Fat-soluble vitamin levels can be reduced in patients suffering from prolonged starvation or malabsorption (especially fat malabsorption). By contrast, the water-soluble vitamins (C, folate, and other B complex vitamins) undergo rapid decline when patients are subjected to dietary deprivation. Table 16-2 provides a list of clinical conditions associated with specific vitamin deficiencies.

Individual deficiencies of the trace minerals, copper, zinc, selenium, chromium, manganese, and molybdenum, have all been associated with specific syndromes. Significant clinical deficiencies of these elements are rare, however, even among the malnourished who receive meager nutritional support. Luckily, all commercially available tube feeding products and now essentially all PN solutions contain at least the daily minimum requirements of vitamins and trace minerals, making clinical deficiencies uncommon.

ROUTES OF NUTRITIONAL SUPPLEMENTATION

Enteral Nutrition Therapy

Enteral nutrition (EN) offers numerous advantages over the parenteral alternative, making it the preferred method of nutrition support (Table 16-3). Its primary benefit is in maintaining gut barrier functions. EN helps maintain tight junctions between intraepithelial cells, lessens gut permeability, and reduces risk for systemic infection. Providing fuel to the GI mucosa also keeps gut-associated lymphoid tissues (GALT) and mucosal-associated lymphoid tissue (MALT), healthy and functioning. Nutrients in the small intestine help maintain normal gallbladder function by stimulating the release of cholecystokinin, thereby reducing risk of cholecystitis.

EN therapy should be considered in any hemodynamically stable critically ill patient unable to begin an oral diet and expected to require an ICU length of stay greater than 2 to 3 days. Contraindications for EN may include severe GI bleeding, severe GI malabsorption, bowel ischemia, bowel discontinuity, mechanical bowel obstruction, or severe ileus. Of themselves, bowel sounds, flatus, or stooling should not be required for initiation of EN. Bowel sounds are only indicative of contractility and do not provide information about the patient's mucosal integrity or absorptive capacity. In addition, gastric peristalsis is often lost during critical illness, despite preserved small bowel function. However, observations regarding bowel functioning should still be monitored when determining tube feeding tolerance.

Table 16-3. Advantages of Enteral Nutrition
Maintains gut mucosal structure
Decreases bacteria and toxin translocation
Supports immune functions
Promotes enteric hormone secretion
Eliminates need for central catheter
Reduced risk of sepsis and line-related complications
Buffers gastric acid
Less likely to induce hyperglycemia
Decreased cost compared with parenteral nutrition

If full enteral feedings are not appropriate, then “trophic” tube feedings may be considered. Trophic feeding is defined as a low-rate EN, typically 10 to 20 mL/h. The purpose of trophic feeding is to provide fuel to the GI mucosal cells and maintain some of the nonnutritive benefits of EN, even if a patient’s full nutritional needs cannot yet be met. Examples of situations where trophic feeding may be used are recent GI surgery with fresh bowel anastomosis, continuous neuromuscular blockade, and increased risk of ileus. If trophic feedings are initiated, efforts to improve adequacy of calorie/protein intake should be made as soon as feasible by increasing tube feeding rate to goal.

**Enteral Nutrition Access and Delivery Method**

The type of enteric access chosen for EN should depend on the patient's disease severity, GI function, anticipated duration of EN support, and institutional resources available for tube placement. If the need for EN is expected to last a relatively short time (<4 weeks) or if duration is unknown, a temporary nasal or oral feeding tube placed into the stomach or small bowel is appropriate. This can be a large-bore (≥14 French) or small-bore (typically 8 to 10 French) tube. Small-bore tubes are usually preferred for comfort, especially if not needed for enteral medications that place the feeding tube at risk of clogging. Small-bore tubes are also chosen when postpyloric, or small bowel, tube placement is preferred. The motility of the stomach may be selectively reduced. Although many nutrition experts agree that it is acceptable to cautiously initiate EN in the stomach (with periodic residual checks), postpyloric placement may be preferred for patients at unusually high risk for aspiration. Potential risks of aspiration are not well defined but may include the presence of a nasogastric or gastroenteric tube, reduced level of consciousness, supine positioning, fixed neurologic deficits, and gastroesophageal reflux. Postpyloric feedings may also be desirable in the patient with an ileus,

as peristalsis of the small bowel generally returns before gastric and colonic motility. Studies have found that patients with feeding tubes placed into the small bowel achieve a greater percentage of their daily nutritional intake goals, likely because of fewer interruptions in feedings. Many providers allow enteral feedings through postpyloric tubes to continue through minor procedures or up until surgery begins. These temporary tubes can be placed at the bedside (often with magnetic tracking) by a trained clinician or under fluoroscopic guidance by a radiologist. Nasal feeding tubes are secured using tape or a retaining device, called a bridle. Before initiating feedings with any tube placed blindly into the GI tract, correct placement should be confirmed radiographically. Tube location should be monitored regularly with visualization of tube at the exit site to ensure that inadvertent tube dislodgement from its
original location has not occurred.

If enteral access is needed for a prolonged period (>4 to 6 weeks), then a more permanent feeding tube should be considered. A gastrostomy tube is appropriate in the patient with a functional stomach, where a jejunostomy or gastrojejunostomy is preferred when delayed gastric emptying is expected or risk of aspiration is high. These tubes can be placed percutaneously with endoscopic guidance, through interventional radiology, or via direct surgical intervention.

<table>
<thead>
<tr>
<th>Formula Type/Characteristics</th>
<th>Patient Uses</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymeric, nutritionally complete oral supplement, 1-1.5 kcal/mL</td>
<td>Oral supplement</td>
<td>Boost, Boost Plus, Ensure, Ensure Plus</td>
</tr>
<tr>
<td>Polymeric, nutritionally complete tube feeding, 1-1.2 kcal/mL</td>
<td>General purpose, normal digestion</td>
<td>Osmolite 1 Cal, Nutren 1.0, Isosource HN, Osmolite 1.2 Cal</td>
</tr>
<tr>
<td>Polymeric, nutritionally complete concentrated tube feeding, 2 kcal/mL</td>
<td>Normal digestion, fluid restricted</td>
<td>Nutren 2.0, TwoCal HN</td>
</tr>
<tr>
<td>Polymeric, nutritionally complete high-protein tube feeding, 1 kcal/mL</td>
<td>High-protein needs</td>
<td>Replete, Promote</td>
</tr>
<tr>
<td>Fiber-containing, nutritionally complete tube feeding, 1-1.2 kcal/mL</td>
<td>Diarrhea or constipation management for long-term tube feeding</td>
<td>Jevity 1 Cal, Jevity 1.2 Cal, Nutren 1.0 Fiber, Fibersource HN</td>
</tr>
<tr>
<td>Peptide-based, nutritionally complete tube feeding, 1-1.2 kcal/kg</td>
<td>Critical illness with impaired GI function</td>
<td>Peptamen AF, Vital AF 1.2 Cal</td>
</tr>
<tr>
<td>Elemental, nutritionally complete tube feeding, 1 kcal/mL</td>
<td>Malabsorption, intestinal failure, chylothorax</td>
<td>Vivonex TEN</td>
</tr>
<tr>
<td>Enhanced arginine, omega-3 fatty acids, nucleotide-containing tube feeding</td>
<td>Immunocompromised (trauma, burns, major elective surgery)</td>
<td>Impact</td>
</tr>
<tr>
<td>Disease-specific tube feeding:</td>
<td>Renal failure</td>
<td>Nepro with Carbsteady, Novasource Renal</td>
</tr>
<tr>
<td>Moderate protein, fluid-restricted, lower in electrolytes (K, Phos, Mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease-specific tube feeding:</td>
<td>Acute lung injury or acute respiratory distress syndrome</td>
<td>Oxepa</td>
</tr>
<tr>
<td>Enhanced omega-3 fatty acids, borage oil</td>
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</table>
Delivery method of EN depends on the type of access chosen, risk of aspiration, and disease state. For the majority of critically ill patients, a continuous infusion of EN formula using a feeding pump is best to reduce risk of aspiration pneumonia and optimize tolerance. Cyclic feedings (e.g., nocturnal infusion) may be considered as oral diet is introduced and tube feedings need to be weaned. Bolus feedings can only be considered for patients with a gastric tube (gastrostomy or nasogastric/orogastric tube) who have good stomach function.

**Selection of Formula**

Numerous products are available to supplement oral diets and provide EN therapy. Selecting an enteral formula depends upon the patient's nutritional needs, as these products differ in their caloric concentration and protein content (Table 16-4). Many nutrition experts recommend using a standard polymeric formula when initiating EN in the ICU setting and avoiding routine use of all specialty formulas. Polymeric formulas contain a balanced amount of protein, fat, and carbohydrate, present as complex molecules. These differ from elemental or semielemental formulas, which contain hydrolyzed proteins (peptides, amino acids) and medium-chain triglycerides as a fat source to help with nutrient digestion and absorption. Elemental and semielemental formulas are designed for patients with gastrointestinal disorders and malabsorption. However, peptide-based formulas have not been extensively studied. Results on incidence of diarrhea with peptide-based formulas versus polymeric formulas have shown mixed results. Virtually all enteral formulas are lactose-free and gluten-free to minimize intolerance.

More recently, immunomodulating formulations have been developed, enriched with ingredients such as arginine, glutamine, nucleotides, and omega-3 fatty acids. These formulas have been the most studied in recent years because of research suggesting that in some patient populations, their use may improve outcomes such as reduced infection, hospital length of stay, and duration of mechanical ventilation. To date, these formulas have shown the most benefit in perioperative patients; thus, they are more appropriate for use in surgical than medical ICU populations.

In specific patient cases, a specialty formula may be preferred over a standard formula. For example, if a patient with renal failure has high serum potassium levels, then a specialized renal formula lower in electrolytes may be desired. In cases where fluid restriction is necessary, a highly concentrated, low fluid-containing formula may be chosen. Fluid-restricted formulas are often thicker and have higher osmolality than standard formulas.

Formulas can be found in fiber-containing and fiber-free versions. Most fiber-containing formulations contain a mix of both soluble and insoluble fiber. Soluble fiber is thought to control diarrhea because of its ability to increase sodium and water absorption, whereas insoluble fiber promotes regular stooling by increasing fecal weight and thus decreasing transit time in the gut. There is concern about the use of mixed-fiber formulas in patients at high risk for bowel ischemia or dysmotility due to reports of bowel obstruction in surgical and trauma patients receiving formulas that contain insoluble fiber. For this reason, nutrition experts recommend the use of fiber-free enteral formulas in conjunction with a soluble fiber supplement in doses of 10 to 20 g/day for hemodynamically stable patients in whom fiber may be beneficial in preventing or reducing diarrhea.

Most enteral formulations provide adequate vitamin and mineral supplementation to meet recommended daily intake amounts when provided in volumes of 1,000 to 1,500 mL/day. If a formula is provided in volumes less than this, then separate vitamin/mineral supplementation may need to be considered.

**Enteral Nutrition Complications**

One of the most feared and serious complications of EN is aspiration of stomach contents into the airway, as it can lead suddenly to pneumonia and acute respiratory distress syndrome (ARDS). Precautions clinicians can take to reduce the incidence of oral as well as gastric aspiration include keeping the patient's head of bed elevated greater than 30 to 45 degrees, using chlorhexidine mouthwash twice daily, reducing the level of
sedation/analgesia when possible, and minimizing transportation out of the ICU for diagnostic tests/procedures. It is also safest to use continuous tube feeding infusion, rather than bolus feedings. For patients at increased risk of aspiration or those who show intolerance to gastric feedings, postpyloric feeding tubes are often preferred. Studies conflict as to whether postpyloric feedings reduce aspiration and pneumonia risk.

The most common problem encountered in the use of EN is putative “intolerance.” Often “intolerance” equates to reluctance to initiate a trial of tube feeding in a patient with mild abdominal distention or minimal bowel sounds. On other occasions, intolerance represents heightened and perhaps excessive concern over an arbitrary “gastric residual volume” or mild abdominal distention. Sometimes, tube feedings are interrupted for gastric residuals as low as 100 mL (seven tablespoons). In general, more liberal limits should be set (e.g., 500 mL) when gastric residual volumes are used to monitor tolerance. There is evidence that gastric residual volumes do not correlate with incidence of aspiration or pneumonia. It may be safe and reasonable to require two consecutive elevated residual volumes before interrupting feeding. When slow gastric emptying is a concern, prokinetic agents (metoclopramide or erythromycin) should be considered. Visual inspection and palpation of the abdomen should be performed routinely in critically ill patients who receive EN, and significant abdominal distention should be evaluated for ileus or obstruction.

Table 16-5. Causes of Diarrhea in ICU Patients

<table>
<thead>
<tr>
<th>MEDICATIONS</th>
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<tbody>
<tr>
<td>Antibiotics</td>
<td></td>
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<tr>
<td>Antidepressants</td>
<td></td>
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<tr>
<td>Antacids (especially those containing magnesium)</td>
<td></td>
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<tr>
<td>Histamine blockers</td>
<td></td>
</tr>
<tr>
<td>Peristalsis-promoting drugs (metoclopramide, erythromycin)</td>
<td></td>
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<tr>
<td>Cholinergic agents (physostigmine, neostigmine)</td>
<td></td>
</tr>
<tr>
<td>Sorbitol-containing oral medicines</td>
<td></td>
</tr>
<tr>
<td>Certain chemotherapy (irinotecan, 5-fluorouracil, capecitabine)</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td></td>
</tr>
<tr>
<td>Stool softeners/laxatives</td>
<td></td>
</tr>
</tbody>
</table>

| COLONIC INFECTIONS            |                |
| Clostridium difficile         |                |
| Enteric pathogens (Salmonella, Shigella, Campylobacter) |                |

| COLONIC IMPACTION (overflow diarrhea) |                |

| MALABSORPTION                  |                |
| Intestinal resection           |                |
| Inflammatory bowel disease     |                |
| Bile acid malabsorption       |                |
| Fatty acid malabsorption      |                |

Diarrhea is a commonly reported GI side effect in patients receiving EN (Table 16-5). Most cases of diarrhea in
enterally fed patients are not due to the tube feeding but rather due to concurrent use of medications (e.g., antibiotics, stool softeners/laxatives) or infection (Clostridium difficile and nonclostridial bacteria). Intolerance to the formulation of the tube feeding is less common, but formula osmolality, delivery rate and mode, and fiber content should be evaluated. Bacterial overgrowth of the GI tract can also cause severe enteritis with diarrhea, a problem sometimes encountered after Roux-en-Y gastric bypass surgery or with prolonged use of broad-spectrum antibiotics. In patients with persistent diarrhea, suspected malabsorption, or lack of response to soluble fiber supplementation, a semi-elemental formula may be tried.

Enteral nutrition contamination is a potential source of pathogenic microorganisms that lead to diarrhea. It is important to use best practices of hand hygiene, clean gloves, and aseptic techniques when enteral formulas are prepared and administered to reduce contamination. Many hospitals now use closed-system EN formulas in prefilled bottles or bags that are accessed with screw tip tubing and reduce risk of outside contamination. Formulas in a closed system can hang for 24 to 48 hours, according to manufacturer recommendations. Care should still be taken to change pump tubing daily. Finally, to the present time there are no convincing data confirming the value of probiotics for patients with or recovering from critical illness.

Feeding tube occlusion is a frequent problem that requires unclogging methods or tube replacement. Small-bore feeding tubes are more prone to issues with clogging. Tube clogs are also more likely to occur with inadequate water flushing and enteral medication delivery. Tactics to unclog a feeding tube include simply flushing with warm water or the instillation of pancreatic enzymes to break up clogs caused by enteral formulas.

Metabolic complications are not as common with EN as with PN but can include those related to refeeding syndrome as well as hyperglycemia. Daily monitoring of electrolytes and serum glucose levels is recommended during initiation of EN. Even with the best of intentions, patients seldom receive the intended daily amount of enteral feeding. Enteral feedings are frequently interrupted for artificially low gastric residual volumes and for tests/procedures that require the patient to remain NPO with tube feedings held. Institutions should develop and implement enteral feeding protocols to prevent recurring failures to reach intended goals for daily calorie and protein intake.

**Parenteral Nutrition Therapy**

Parenteral nutrition (PN) is an intravenous nutrition solution that should be reserved for patients with a dysfunctional, limited, or nonusable gut. Examples of conditions where PN may be indicated are short bowel syndrome, mesenteric ischemia, complete bowel obstruction, severe prolonged ileus, and intestinal fistulas. However, every case should be evaluated individually and EN options ruled out before PN is considered. There are no demonstrated benefits of intravenous nutrition over EN if the latter can be accomplished. PN therapy is more costly and more commonly associated with metabolic and infectious complications than EN. PN solutions may be delivered into peripheral or central veins, with each route having specific advantages and disadvantages.

The appropriate time to initiate PN support in the critically ill patient has been a topic of debate. Many nutritionists recommend withholding PN during the first week of hospitalization for patients who were well nourished prior to admission. This recommendation changes if a patient is admitted to the ICU already severely malnourished and EN is not possible. In this case, PN should be considered much earlier in the patient's ICU course.

Parenteral nutrition can also be considered when EN support has repeatedly failed to meet the patient's nutritional needs because of intolerance or complications. One organizational guideline is to consider PN after 7 to 10 days if unable to meet greater than 60% of energy and protein requirements by the enteral route alone.

**Central Parenteral Nutrition**
Central parenteral nutrition (CPN) is often referred to as total parenteral nutrition (TPN) because a patient's full nutritional needs, including macronutrients and micronutrients, can potentially be met by this route alone. CPN is preferred for use in patients who will require PN for longer than 7 to 14 days. CPN includes a balanced formulation of dextrose, amino acids, IV fat emulsion, electrolytes (sodium, potassium, magnesium, phosphorus), vitamins, and trace elements. The osmolarity of these solutions is typically very high (1,300 to 1,800 mOsm/L) and therefore must be administered through central venous access. CPN can be prepared as a 3-in-1 admixture (also called TNA, total nutrient admixture), where the fat emulsion is compounded in the same container as the other nutrients, or as a 2-in-1 solution in which the fat emulsion is provided as a separate infusion from the other nutrients. Some institutions use standardized commercially available PN solutions, whereas, others have the ability to customize PN solutions to the patient's specific macronutrient and micronutrient requirements and compound the solution in-house.

If ordering a customized PN solution, care should be taken to order macronutrients in quantities that reduce metabolic complications. Carbohydrate (dextrose) administration should not exceed a rate of 4 to 5 mg/kg/min or 20 to 25 kcal/kg/day. Protein content should meet the patient's estimated protein needs, which are typically 1.2 to 2.0 g/kg in critical illness. IV fat emulsion should be restricted to less than 30% total calories or 1 g/kg/day to prevent hypertriglyceridemia. Daily electrolyte requirements include 1 to 2 mEq/kg sodium, 1 to 2 mEq/kg potassium, 10 to 15 mEq/day calcium, 8 to 20 mEq/day magnesium, 20 to 40 mmol/day phosphorus, and chloride and acetate as needed to maintain acid-base balance. Commercially available vitamin and trace element packages are also added in predetermined quantities.

**Peripheral Parenteral Nutrition**

Peripheral parenteral nutrition (PPN) may be considered in patients requiring PN for a short duration, between 5 and 14 days. PPN requires a lower concentration of nutrient components than a centrally provided PN solution to assure that osmolarity (600 to 900 mOsm/L) is acceptable for peripheral venous administration. Because of the lower concentration of nutrients per liter, large fluid volumes (often >2.5 to 3 L/day) of PPN are needed to meet a patient's full nutritional needs. For this reason, PPN is not a good option for patients who need fluid restriction.

Although it is advantageous to avoid the infectious, thromboembolic, and mechanical risks of placing a central line required for CPN, the corrosive nature of the PPN solution presents a problem for peripheral administration. Venous inflammation often results from the high osmolarity and potassium content of PPN solutions. Used alone, glucose and amino acid mixtures are highly irritating, and extravasation must be avoided. Concurrent infusion of IV fat emulsion with the PPN solution reduces the risk of chemical phlebitis, as well as provides another calorie source for the PN solution. Peripheral intravenous sites should be changed at least every 48 to 72 hours, and the use of this therapy should be limited to 2 weeks' duration. Because of the numerous practical problems of PPN, it is seldom used.

**Complications of Parenteral Nutrition**

Complications of PN are reduced by an experienced team versed in all aspects of PN, including the local care of infusion catheters. Catheter tip position must be checked before starting feeding to prevent inadvertent infusion of fluids into the pericardium or pleural space. Placing a central line for PN therapy carries with it all the infectious risks of this type of line placement. To reduce the risk of catheter-related bloodstream infections, the Institute for Healthcare Improvement has proposed a set of evidence-based practices, which includes (1) hand hygiene, (2) maximal barrier precautions, (3) chlorhexidine gluconate (CHG) skin antisepsis, (4) optimal catheter site selection, and (5) daily review of need, with prompt removal of unnecessary lines. Apart from line care, another way to prevent infectious complications is to observe sterile procedures for PN formula compounding and ensuring that the “hang time” of PN solutions does not exceed 30 hours or 12 hours for IV fat emulsions. Metabolic complications are more common with PN than with EN. Patients receiving PN require close monitoring of capillary glucose levels, serum electrolytes, liver function tests (LFTs), and other laboratory values for prevention and early detection of
complications. In the ICU environment, daily weights should also be obtained to monitor fluid status.

Metabolic complications are more likely to occur in starved and severely malnourished patients and in those with diabetes or impaired hepatic or renal function. As discussed previously, sudden refeeding in a malnourished patient can trigger fluid and electrolyte shifts, referred to as refeeding syndrome. Risk can be reduced when malnourished patients are introduced to nutrition support cautiously, starting with a lower calorie level and advancing slowly. For those at high risk, electrolytes need to be checked relatively frequently.

Hyperglycemia is a common complication of PN, which is exacerbated by the stress-associated hyperglycemia often seen in critically ill patients. Carbohydrate infusion may need to be limited in the patient with severe hyperglycemia until blood glucose levels are under better control. Insulin can be added directly to the PN solution or given separately. Care should be taken to avoid hypoglycemia when PN is tapered or discontinued in patients receiving insulin. A 1- to 2-hour taper using half the prior infusion rate may reduce the risk of rebound hypoglycemia.

Hypertriglyceridemia can occur with overfeeding of dextrose or rapid infusion of IV fat emulsion. Avoiding overfeeding of both dextrose and lipid and administering IV fat emulsion over no less than 8 to 12 hours will help reduce this complication risk. Serum triglyceride levels should be checked weekly with acceptable levels less than 400 mg/dL.

There is concern about the use of soybean oil-based IV fat emulsions with PN solutions in critical illness, owing to their potentially pro-inflammatory properties. For this reason, some experts suggest withholding or limiting soy-based fat emulsions the first week following initiation of PN in the ICU, providing a maximum of 100 g/week if there is concern for essential fatty acid deficiency. Alternative fat emulsion products (containing medium-chain triglycerides, olive oil, and fish oil emulsions) are now available that provide a superior source of lipid calories.

Disorders of the liver and biliary system are commonly encountered with PN. These include gallbladder sludge/stones, cholestasis, and steatosis. Acalculous cholecystitis and cholelithiasis during PN therapy are likely observed because of the lack of enteral stimulation and diminished gallbladder secretion and emptying. PN-associated cholestasis and steatosis more likely relate to the PN therapy itself. Lipid administration encourages cholestasis by inhibiting hepatic bilirubin excretion. Restricting lipid intake to less than 1 g/kg/day may help prevent this problem. Steatosis, or hepatic fat accumulation, typically presents as elevations in liver enzyme concentrations and is thought to be a result of overfeeding.

High insulin levels produced by continuous glucose infusion may inhibit lipolysis and favor triglyceride synthesis. The PN solution should be evaluated to ensure there is a good balance of carbohydrate and fat (70% to 85% of nonprotein calories as carbohydrate and 15% to 30% as fat) and that carbohydrate content does not exceed 7 g/kg/day. Another strategy to manage PN-associated liver complications is cycling PN to allow time for the liver the "rest" each day, which has been shown to reduce serum liver enzymes and conjugated bilirubin levels. Even when PN solutions are continued, LFT abnormalities often revert to normal in a few weeks.

**DISEASE-SPECIFIC CONSIDERATIONS**

**Pulmonary Failure**

Malnutrition is a risk factor for the development of pulmonary complications in the critically ill patient, and the onset of pulmonary failure can further worsen a patient's nutritional status if protein/calorie support is inadequate. Providing the appropriate caloric support is especially important in the patient with pulmonary failure, as underfeeding can lead to diminished muscle strength and prolong weaning from ventilator support. On the other hand, overfeeding can also have consequences. Overfeeding stimulates excessive CO₂ production, further stressing a limited excretory capacity for CO₂. Overfeeding also increases lipogenesis, encourages hyperglycemia, and potentially compromises a patient's ability to wean from the ventilator. It was previously believed that feeding
patients a high-fat, low-carbohydrate diet or enteral formula would prevent the problem of excessive CO₂ production in this patient population, but more recent studies have concluded that these specialty formulas only decreased CO₂ production in patients who were being overfed. Therefore, the current recommendation for reducing CO₂ production in the critically ill patient with pulmonary failure is simply to avoid overfeeding and that a high-fat/low-carbohydrate formula is not needed.

Acute respiratory distress syndrome is an inflammatory disorder with high oxidant stress. Because survivors typically require more than a week of ventilation, they are often provided nutritional support. ARDS patients have been reported to have reduced plasma levels of specific omega-3 (n-3) fatty acids (i.e., eicosapentaenoic acid and docosahexaenoic acid) and proportionally higher levels of the omega-6 (n-6) arachidonic acid. This observation is of interest, because arachidonate metabolism yields highly inflammatory dienoic prostaglandins and 4-series leukotrienes, whereas n-3 fatty acid metabolism produces less-inflammatory trienoic prostaglandins and 5-series leukotrienes. Studies have been conducted to evaluate the clinical outcomes of ARDS patients fed with an enteral formula characterized by an anti-inflammatory lipid profile (rich in omega-3 fatty acids) and antioxidants. Results have been conflicting.

Renal Failure

Acute renal failure by itself has little impact on resting rates of energy expenditure. However, the physiological stress of associated medical conditions or the type of renal replacement therapy a patient receives can increase caloric and protein needs. Providing sufficient nutrition is important to promote renal function recovery and may decrease the degree of protein catabolism. Metabolic abnormalities associated with acute kidney injury include glucose intolerance, fluid overload, decreased protein synthesis, increased protein catabolism, metabolic acidosis, and electrolyte abnormalities resulting from impaired excretion of potassium and phosphorus. Accumulating by-products of protein metabolism increase blood urea nitrogen. Historically, it was felt that protein restriction was necessary to reduce azotemia and the progression of renal failure, but the importance of nutrition in supporting the patient's metabolic needs is now recognized to take precedence. Current recommendations are to provide patients with their full estimated needs and to use dialytic support to remove the generated waste, if necessary. When enteral support is chosen and renal replacement therapy has not been started, there are numerous commercially available concentrated products high in calories but low in potassium and phosphorus to meet patient needs. In the patient receiving renal replacement therapy, protein, fluid, and electrolyte losses may be quite significant, allowing tolerance of a standard enteral formula.

Finally, protein losses from renal replacement therapy should be considered for both acute and chronic renal failure. Protein need for the unstressed patient on hemodialysis is estimated to be 1.2 to 1.3 g/kg/day. However, in the metabolically stressed critically ill patient, these needs could increase to 1.5 to 1.8 g/kg/day. Continuous renal replacement therapy is associated with a 10- to 15-g/day amino acid loss, and protein needs can reach 2.5 g/kg/day in the highly catabolic patient. Although it is important to meet a patient's protein needs, providing excess protein should be avoided, as it may simply increase the rate of urea production.

Hepatic Failure

Malnutrition that correlates with disease severity is prevalent among patients with chronic liver failure. The cause of malnutrition is often multifactorial and can be attributed to decreased oral intake (due to alterations in taste, early satiety, nausea, gastroparesis, and slow intestinal motility), maldigestion and malabsorption, as well as metabolic abnormalities. In patients with advanced liver disease, it is important to minimize periods of time without nutritional intake, as decreased glucose oxidation and increased protein and fat catabolism quickly place patients into a state mimicking starvation.

Patients with hepatic failure are predisposed to complications of ascites, edema, intravascular volume depletion, and hypoalbuminemia. As a result, it is not uncommon for a patient's weight to fluctuate because of fluid status.
When estimating nutritional needs, a usual weight or dry weight should be used, and protein needs approximate 1.0 to 1.5 g/kg/day. In the past, protein restriction was suggested as a way to reduce hepatic encephalopathy. However, protein restriction can lead to worsening nutritional status, loss of lean body tissue, and even impaired ammonia removal. If EN therapy is indicated, it is recommended to use standard enteral formulations. There is no evidence of benefit from formulas high in branched chain amino acids in the ICU patient with encephalopathy who is already receiving treatment with luminal-acting antibiotics and lactulose.

**Pancreatitis**

Enteral nutrition is the preferred form of nutrition support therapy in the patient with acute pancreatitis when eating is not feasible. In fact, critically ill patients with moderate to severe acute pancreatitis should be considered for early EN support therapy (within 24 to 48 hours of admission). When compared to the parenteral alternative, EN has been found to reduce infection morbidity, hospital length of stay, and need for surgical intervention in these patients. Although some research indicates no difference in tolerance or clinical outcome with gastric versus jejunal feeding, one strategy to improve enteral tolerance is to infuse more distally in the GI tract (beyond the ligament of Treitz if possible) to decrease pancreatic stimulation. Nutrition experts recommend the use of a standard polymeric formula. However, if there is intolerance to EN, or if maldigestion/malabsorption is suspected, a small peptide formula with medium-chain triglycerides or a low-fat elemental formula may be indicated.

**Burns**

Burned patients have very high caloric requirements and protein losses during the hyperacute phase of care. Recommendations for protein intake in this patient population are 1.5 to 2.0 g/kg/day or 20% to 25% of calories from protein. EN is the preferred route for supplementation, with evidence that supports very early initiation of EN (<24 hours after injury) to blunt the metabolic response to this stress and improve clinical outcomes. Glutamine supplementation may benefit burn-injured patients by helping preserve mucosal barrier function and diminishing infectious complications, with recommended enteral doses of 0.3 to 0.5 g/kg/day. Adequate vitamin supplementation is also critical in these patients with increased needs for healing.

**SUGGESTED READINGS**


Chapter 17

Analgiesia, Sedation, Neuromuscular Blockade, and Delirium

• Key Points

1. Analgesia, rather than sedation, is the first line of measures taken to assure comfort and cooperation. When used at all, sedatives should be administered to achieve specific target levels of an objective sedation scale and should be interrupted at least once daily as part of a planned spontaneous awakening trial in the majority of ventilated patients.

2. Agitation is often a manifestation of discomfort or physiologic distress that can be resolved without the use of pharmacologic agents. Ventilator adjustments, repositioning, relief of GI or bladder distention, and reassurance are essential nonpharmacologic methods of agitation management.

3. Once stabilized, many patients receiving opiates require little or no sedation.

4. When pharmacotherapy is deemed necessary, drug selection should be based on desired effect, duration of action, and economic and physiologic costs that relate to organ dysfunction. In general, intermittent (as opposed to continuous) dosing of longer-acting compounds is the preferred strategy to smooth peak and trough effects, prevent oversedation, and reduce costs.

5. Most drugs have longer duration of action and a larger volume of distribution when given to ICU patients than to those less seriously ill.

6. A narcotic (morphine or fentanyl) with a benzodiazepine (lorazepam) offers a safe, effective, economical short-term analgesic-sedative combination for many ICU patients. Nonopioid analgesics may be considered to reduce opioid dosing and related side effects.

7. Typical antipsychotic agents often play a valued role in longer-term sedation.

8. Propofol is a good choice for intermediate-term sedation (hours) and for sedating hemodynamically tolerant patients with neurological conditions requiring frequent reassessment. Sedation with dexmedetomidine may be preferred over sedation with benzodiazepines to improve clinical outcomes in mechanically ventilated patients.

9. Haloperidol is often but not invariably effective for extremely agitated or delirious patients not experiencing pain.

10. Neuromuscular blockers should be used judiciously and for relatively brief periods because risks include awake paralysis, hemodynamic instability, prolonged muscle weakness, and concealment of intercurrent illness. When necessary for long-term neuromuscular blockade, pancuronium and vecuronium are safe, economical choices for most patients.

11. Delirium is now recognized as a frequent and serious problem in critically ill patients. There is no diagnostic test which confirms the diagnosis; thus, clinical criteria are employed. Risk factors include advanced age, neurologic injury, and increased severity of illness.

12. Two forms of delirium are encountered: the hypoactive and the less common agitated (or hyperactive) variants. Mixed delirium displays elements of both forms. Although some evidence indicates that antipsychotic agents and dexmedetomidine are better than benzodiazepines from the standpoint of delirium incidence, these data are limited and inconsistent.

13. The best management of delirium is prevention by prompt pain management, limited administration of sedation, reorientation, and early mobilization.

GOALS OF THERAPY

The relief of pain and anxiety is often overlooked, when efforts focus on the life-threatening crisis. A growing awareness of the stress imposed by the intensive care unit (ICU) and the increasing popularity of some modes and settings for mechanical ventilation that are intolerable without sedation have highlighted the need for effective pharmacotherapy. In the ICU, the overall goal is to use just enough of an optimally chosen sedative and/or analgesic for the shortest possible time. Doing so avoids immediate deleterious cardiopulmonary effects and minimizes adverse neuropsychological and muscular effects. Patients not receiving neuromuscular blockade should be maintained comfortable but ideally maintained sufficiently alert to communicate their needs and cooperate in their care. By contrast, adequate analgesia and sedation to unconsciousness are mandated during neuromuscular blockade in all but the most exceptional circumstances. Reluctance to provide analgesia or sedation to nonintubated patients is understandable but has its own liabilities; withholding medication can result in unrelieved pain and anxiety and cause splinting, atelectasis, and increased O₂ consumption. Inadequate analgesia discourages activity, promoting venous thrombosis and deconditioning.

MONITORING TREATMENT

It has become clear that poorly regulated or monitored sedation exacts a high price by increasing sedative costs, predisposing patients to delirium, prolonging ventilator time, and even increasing mortality. In the short term, excessive sedation causes respiratory depression, hypotension, and gastrointestinal (GI) hypomotility. Immobility often masks the presence of intercurrent illnesses. Over the long-term, excessive sedation results in cognitive impairment and encourages muscular deconditioning. There are several effective strategies to minimize the adverse effects of sedatives and analgesics. One measure is to begin therapy using intermittent doses instead of continuous infusion. (Propofol and dexmedetomidine are obvious exceptions.) If intermittent doses of analgesics or sedatives are being given more frequently than every 2 to 3 hours, it makes sense to transition to continuous infusion. Continuous infusions should only be used when needed by the patient, not for the convenience of the staff. Continuous infusions have been associated with higher total medication doses and longer duration of mechanical ventilation. Another strategy to avoid excessive sedation or analgesia is to use a well-validated assessment scale. For sedation measures, such as the Richmond Agitation and Sedation Scale (RASS) or the Sedation-Agitation Scale (SAS), targets selected by a physician are achieved by nurses giving carefully considered doses of sedatives. Incorporating a review of the current RASS/SAS versus target RASS/SAS into rounds each day helps align physician and nurse goals and holds each accountable to a realistic objective and means to achieve it. In some ICUs, Bispectral Index (BIS) monitoring has been implemented in an attempt to prevent inadequate sedation of paralyzed patients. Although unlikely to be harmful, the usefulness of BIS monitoring is uncertain; recent reports suggest awareness is possible despite BIS scores that would suggest otherwise. It has also been recognized that artifact can increase the BIS score, falsely suggesting awareness and perhaps prompting unnecessary sedative administration. Hence, BIS monitoring should not replace clinical (e.g., pulse, blood pressure, observational) monitoring.

In addition to the use of an objective sedation scale, daily sedation-free periods (spontaneous awakening trials) facilitate recognition of the time when less sedative is needed. In several clinical trials, scheduled sedation interruption results in fewer days of ventilation, fewer days in the ICU and hospital, and fewer neurological evaluations. A growing body of evidence regarding spontaneous awakening suggests that mortality may be reduced by this practice. Current data suggest that sedation interruption does not increase neuropsychological or physiologic risks.

CORRECTABLE FACTORS CAUSING AGITATION

Initially, agitation should not be regarded as a “sedative deficiency” but rather as a potential sign of unrelieved pain or physiologic or psychological distress. Hence, before sedating or paralyzing agitated patients, especially those being mechanically ventilated, it is critical that common correctable problems be excluded (Table 17-1). Difficulty
interfacing with the ventilator shortly after intubation is often improved by suctioning and adjusting the mode of ventilation, tidal volume, flow rate, and/or trigger sensitivity (see Chapters 7 and 8 on mechanical ventilation). Often, nonpharmacologic actions such as reorientation, reassurance, repositioning, and relaxation therapy suffice.

### Table 17-1. Correctable Factors Causing Agitation

<table>
<thead>
<tr>
<th>Endotracheal tube malposition or obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoemia</td>
</tr>
<tr>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Ventilator malfunction</td>
</tr>
<tr>
<td>Stomach, bowel, or bladder distension</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Impaired communication</td>
</tr>
<tr>
<td>Sleep deprivation</td>
</tr>
</tbody>
</table>

### CHOOSING PHARMACOLOGIC AGENTS

The choice of an analgesic, sedative, or neuromuscular blocker and its dosage and route of administration should be based on the desired duration of effect, pharmacologic properties of the drug, and individual patient factors. The most common errors in initial sedative analgesic selection are insufficient doses given too infrequently and use of short-acting agents when longer duration is required. Although use of short-acting agents offers the theoretical advantage of sedation titration, in most cases, rapid reversal of sedation is unnecessary. Furthermore, inadequate sedation occurs commonly with short-acting drugs, and prolonged infusions of short-acting drugs often result in drug accumulation and undesired prolongation of effect. Using short-acting drugs for long-term sedation is often costly (sometimes hundreds or even thousands of dollars per day). The most common error during ongoing sedation is to minimize sedative dosing and to forego interruption therapy. Such errors typically reflect not regularly reassessing the patient using an objective sedation scale.

### Analgesics

**Opioids**

Opioids are potent, predictable, and reversible analgesics but are poor amnestic agents. When analgesic doses of opioids are used alone, few hemodynamic or respiratory effects are observed; however, when large “anesthetic-range” doses (often 10 times the analgesic dose) are used or when narcotics are combined with neuromuscular blockers or other sedatives, the risk of cardiopulmonary instability increases. Opioid complications are minimized by (1) insuring that intravascular volume is adequate, (2) using the lowest effective dose, and (3) slow administration. The histamine-releasing (vasodilating) potential of opioids is minimal unless large intravenous (IV) doses are given rapidly (meperidine and morphine are the most well-documented offenders). Although rarely necessary, histamine effects can be attenuated by pretreatment with H1 and H2 blockers. A feature common to all narcotics is blunting of the hypercapnic and hypoxic respiratory drives. Although often considered a liability, reducing the respiratory drive often benefits mechanically ventilated patients by decreasing the dyspnea, reducing minute ventilation requirements, encouraging slow deep breathing, and diminishing the tendency for breath stacking. Blunting respiratory drive provides needed comfort for dyspneic patients near the end of life.

Unfortunately, opioids and their breakdown products accumulate in patients with hepatic and/or renal failure, especially in those receiving prolonged treatment. Hepatic biotransformation typically precedes renal excretion of drugs and their metabolites. Initially, the synthetic, highly lipid-soluble opioids (e.g., fentanyl, sufentanil, alfentanil) have their actions countered by redistribution, not metabolism. With chronic use, however, patients become “saturated” with the drug, requiring metabolism for termination of effect. Another synthetic opioid, remifentanil, has its effects terminated within minutes by rapid plasma esterase metabolism. Opioids, especially in high doses, may complicate attempts at enteral feeding by reducing GI motility and inciting nausea. Recent reports suggest that subcutaneous administration of the μ receptor antagonist methyllyctroxine may attenuate this effect. Regional and epidural blocks, patient-controlled analgesia, multimodal analgesia using nonopioid analgesics (e.g., ibuprofen), and addition of anxiolytic agents, which potentiate analgesics (e.g., benzodiazepines), are significant advances in pain control, providing superior relief with a lower total narcotic dose and lower risk of oversedation. There is a growing appreciation that withdrawal symptoms do occur in long-term recipients of high doses of opioids who have their therapy abruptly discontinued. Withdrawal syndromes in the ICU occasionally masquerade as infection because they can manifest as fever, tachycardia, tachypnea, agitation, and confusion.

Morphine is an inexpensive drug with a rapid onset of action and a 1- to 3-hour half-life. Intermittent IV doses of 2 to 10 mg or 1 to 3 mg/h (0.03 to 0.15 mL/kg/h) by constant infusion usually are adequate for relief of moderate to severe pain in the average adult. Although morphine is an excelle

### Fentanyl

analogic, high doses or the addition of a benzodiazepine is usually required to produce unconsciousness. Morphine action is prolonged by both renal and hepatic failure. Although a fraction of each morphine dose is directly excreted unchanged by the kidney, most is metabolized by the liver before renal excretion. One advantage of morphine over synthetic opioids, especially in the oliguric patient, is its high water solubility, permitting analgesia to be administered in a minimum volume. Hydromorphone is an even more potent (approx. 10-fold) semisynthetic opioid derived from morphine. Its half-life of 2 to 3 hours provides a similar or slightly longer analgesic effect than morphine. However, because the half-life of hydromorphone can increase 20-fold in patients with renal failure, special caution must be exercised in this population.

Fentanyl is a potent, highly lipid-soluble, synthetic opioid possessing a very rapid onset and brief duration of action—at least with initial use. With repeated injections or when given by continuous infusion, large stores of drug may accumulate in fatty tissues that then must be metabolized to terminate drug action. Because of this accumulation, effective half-life of fentanyl after days of use may exceed that of morphine. Initial analgesic doses of 0.5 to 10 μg/kg IV may be titrated upward as necessary. Because fentanyl cannot be prepared in highly concentrated aqueous solutions, it is one of the few analgesic medications that can present a “volume” load. With chronic use, it is common to require several hundred milliliters of fluid each day to administer an effective dose. Fentanyl’s perceived chief advantage is its minimal hemodynamic effect at effective levels of analgesia. Very rarely, fentanyl causes seizures or a bizarre syndrome of chest wall rigidity (most common when large IV doses are given rapidly to elderly patients). Thoracic rigidity may be so severe that intubation, neuromuscular blockade, and mechanical ventilation are necessary. Transdermal patches bypass the substantial first-pass hepatic clearance seen with IV dosing, offering a useful alternative method of administration. Unfortunately, the skin slows diffusion, resulting in a long lag time between patch application and effective analgesia, and removal of the patch fails to rapidly terminate drug effect because the skin serves as a “reservoir.” For patients with modest analgesic requirements and good perfusion, the patch delivery system is worth considering. A relatively high incidence of nausea has been reported with transdermal dosing.

### Alfentanil

Alfentanil is a short-acting, lipid-soluble, synthetic opioid that is more potent than morphine but less so than fentanyl. Consciousness returns rapidly after high doses, making this drug useful for brief but painful procedures. Absence of active metabolites results in minimal drug accumulation unless hepatic failure is present. Sufentanil is perhaps 1,000 times as potent as morphine but, except for a potentially smaller volume requirement, does not offer any significant advantages over fentanyl. Remifentanil, also very potent, short-acting, synthetic opioid, has its effects terminated within minutes by rapid plasma esterase metabolism. Opioids, especially in high doses, may complicate attempts at enteral feeding by reducing GI motility and inciting nausea. Recent reports suggest that subcutaneous administration of the μ receptor antagonist methyllyctroxine may attenuate this effect. Regional and epidural blocks, patient-controlled analgesia, multimodal analgesia using nonopioid analgesics (e.g., ibuprofen), and addition of anxiolytic agents, which potentiate analgesics (e.g., benzodiazepines), are significant advances in pain control, providing superior relief with a lower total narcotic dose and lower risk of oversedation. There is a growing appreciation that withdrawal symptoms do occur in long-term recipients of high doses of opioids who have their therapy abruptly discontinued. Withdrawal syndromes in the ICU occasionally masquerade as infection because they can manifest as fever, tachycardia, tachypnea, agitation, and confusion.

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### Meperidine

Meperidine should be avoided. It is a poor pain reliever and offers no substantial advantage over other opioids, and its myocardial depressant effect and vagolytic and histamine-releasing tendencies often cause tachycardia and hypotension. The perceived superiority of meperidine for patients with ureteral or biliary colic is unfounded. The major metabolite, normeperidine, is active, accumulates in fat, and causes seizures when present in high concentrations.

Despite introduction of new agents, opioids such as fentanyl, hydromorphone, methadone, morphine, and remifentanil are the primary medications for managing pain in critically ill patients. The optimal choice of opioid and dosing regimen utilized for an individual patient depends on factors including the drug pharmacokinetic and pharmacodynamic properties.
Characteristics of commonly used opioids are summarized in **Table 17-2**.

### Reversing Opioid Effects

In the event of opioid overdose, the antagonist naloxone promptly reverses excessive sedation. IV doses of 0.4 to 2 mg are usually sufficient, at least transiently, although doses as high as 10 mg are occasionally required. Naloxone given in repeated smaller doses or by slow IV infusion can undo the respiratory depressant and hypotension causing effects of narcotics without reversing the analgesia. Low-dose naloxone is particularly useful for chronic opioid users who unintentionally develop excessive sedation and/or hypotension. Duration of action for naloxone is not as long as many commonly used opioids, necessitating close observation and sometimes repeated administration to prevent recurrence of sedation.

### Table 17-2.

<table>
<thead>
<tr>
<th>Opiates</th>
<th>Equianalgesic Dose (mg)</th>
<th>IV</th>
<th>PO</th>
<th>Onset (IV)</th>
<th>Elimination Half-Life</th>
<th>Context-Sensitive Half-Life</th>
<th>Metabolic Pathway</th>
<th>Active Metabolites</th>
<th>Intermittent Dosing</th>
<th>IV Infusion Rates</th>
<th>Side Effects and Other Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fentanyl</strong></td>
<td>0.1</td>
<td>N/A</td>
<td>N/A</td>
<td>1-2 min</td>
<td>2-4 h</td>
<td>N-dealkylation CYP3A4/5</td>
<td>None</td>
<td>0.35-0.5 μg/kg IV q0.5-1 h</td>
<td>0.7-10 μg/kg/h</td>
<td>Less hypotension than with morphine. Accumulation with hepatic impairment</td>
<td></td>
</tr>
<tr>
<td><strong>Hydromorphone</strong></td>
<td>1.5</td>
<td>7.5</td>
<td>5-15 min</td>
<td>2-3 h</td>
<td>N/A</td>
<td>Glucuronidation</td>
<td>None</td>
<td>0.2-0.6 mg IV q1-2 h</td>
<td>0.5-3 mg/h</td>
<td>Therapeutic option in patients tolerant to morphine/fentanyl. Accumulation with hepatic/renal impairment.</td>
<td></td>
</tr>
<tr>
<td><strong>Morphine</strong></td>
<td>10</td>
<td>30</td>
<td>5-10 min</td>
<td>3-4 h</td>
<td>N/A</td>
<td>Glucuronidation</td>
<td>6- and 3-glucuronide metabolite</td>
<td>2-4 mg IV q1-2 h</td>
<td>2-30 mg/h</td>
<td>Accumulation with hepatic/renal impairment. Histamine release.</td>
<td></td>
</tr>
<tr>
<td><strong>Methadone</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>1-3 d</td>
<td>15-60 h</td>
<td>N/A</td>
<td>N-dealkylation CYP3A4/5, 2D6, 2B6, 1A2 substrate</td>
<td>N-dealkylated derivative</td>
<td>IV/PO: 10-40 mg q6-12 h IV: 2.5-10 mg q8-12 h</td>
<td>Not recommended</td>
<td>May be used to slow the development of tolerance where there is an escalation of opioid dosing requirements. Unpredictable pharmacokinetics; unpredictable pharmacodynamics in opiate naïve patients. Monitor QTc.</td>
<td></td>
</tr>
<tr>
<td><strong>Remifentanil</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>1-3 min</td>
<td>3-10 min</td>
<td>3-4 h</td>
<td>Hydrolysis by plasma esterases</td>
<td>None</td>
<td>N/A</td>
<td>Loading dose: 1-5 μg/kg IV Maintenance dose: 0.5-15 μg/kg/h IV</td>
<td>No accumulation in hepatic/renal failure. Use IBW if body weight &gt;130% IBW.</td>
<td></td>
</tr>
</tbody>
</table>

*a After 12 h, and in cases of end-organ dysfunction, the context-sensitive half-life increases unpredictably.

*b May increase dose to extend dosing interval: hydromorphone 0.5 mg IV every 3 h, or morphine 4-8 mg IV every 3-4 h.

*c Equianalgesic dosing tables may underestimate the potency of methadone. The morphine- or hydromorphone-to-methadone conversion ratio increases (i.e., the potency of methadone increases) as the dose of morphine or hydromorphone increases. The relative analgesic potency ratio of oral to parenteral methadone is 2:1, but the confidence intervals are wide.

*d QTc is the Q-T interval (corrected) of the electrocardiographic tracing.

IBW, ideal body weight; N/A, not applicable; PO, oral.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are often avoided in the ICU because of their antiplatelet activity and reputation to cause bleeding and renal insufficiency. The frequency and severity of these adverse events are overestimated, and unfortunately drugs with more serious side effects are often chosen as alternatives. Oddly, NSAIDs are often blamed when renal insufficiency develops in patients with multiple potential causes of kidney injury (e.g., low cardiac output, hypotension, contrast exposure, high-dose vasoconstrictors, angiotensin converting enzyme [ACE] inhibitors). Although the cyclooxygenase and platelet-inhibiting activities make NSAIDs less than ideal choices for patients with impaired renal function, coagulopathy, or active bleeding, antiplatelet activity may be advantageous for patients with ischemia. These potent, inexpensive compounds (e.g., aspirin, ibuprofen, and other COX-2 inhibitors) often suffice for pain relief and act synergistically with narcotics (in studies of postoperative pain, opioid doses may be reduced by 1/4 to 1/3). Most NSAIDs can only be given via the GI tract. However, ibuprofen is well absorbed from the rectum, and a liquid formulation may be used in patients unable to tolerate gastric administration. Ketorolac, an effective alternative, is also offered in parenteral form.

**Nonopiod Analgesics**

Several other types of analgesics or pain-modulating agents have been proposed as adjunctive pain medications to reduce opioid requirements. There are limited data on their safety and effectiveness as sole agents for pain management in critically ill patients. For example, IV acetaminophen has been shown to be effective and safe when used in conjunction with opioids for postoperative pain, but caution is advised in the presence of liver dysfunction. Neuropathic pain, often poorly responsive to opioids alone, may be treated with enterally administered gabapentin and carbamazepine in ICU patients with adequate GI absorption and motility. Ketamine, a long available nonopioid analgesic with rapid onset of action, is gaining popularity for procedural analgesia, for support of intubation, and for addressing or averting acute tolerance to opioids. Ketamine may cause hallucinations and other psychological disturbances but may be titrated to a safe level of effectiveness during IV infusion.

A summary of nonopioid analgesics is provided in Table 17-3. It is important to note that pharmacologic treatment principles extrapolated from non-ICU studies may not be applicable to critically ill patients. This table summarizes available consensus data.

**Sedatives**

**Benzodiazepines**

Benzodiazepines are sedative, anxiolytic amnestic with a wide therapeutic margin. Because pain and anxiety are synergistic and often indistinguishable, benzodiazepines can reduce analgesic needs even though they have no intrinsic analgesic properties. Benzodiazepines also induce amnesia and provide anticonvulsant and muscle relaxant properties. Although not as potent as barbiturates or propofol for the purpose, benzodiazepines reduce cerebral O₂ consumption, intracranial pressure, and cerebral blood flow. Although they may induce unconsciousness, this state is not normally slumber. Sleep fragmentation occurs with disrupted range and depth of normal sleep stages. When sleep is the primary objective, a hypnotic may be a better choice than a benzodiazepine intended for sedation (e.g., midazolam, lorazepam, or diazepam). Benzodiazepines are associated with the development of delirium in the critically ill and elderly and, paradoxically, can excite patients by disinhibiting normal social behavioral control. Similarly, amnestic and dissociative effects may linger after consciousness returns, resulting in an agitated, confused state that prompts additional doses of the medication that precipitated it—a potentially vicious cycle. Haloperidol is one agent that allows the practitioner to break this sequence.

Unless used in large doses or combined with narcotics, propofol, or neuromuscular blockers, benzodiazepines have few cardiovascular effects. Mild tachycardia and minimal reduction in blood pressure are most commonly observed in elderly or dehydrated patients, patients using β-blockers, and patients with underlying cardiac disease. Benzodiazepines cause mild dose-dependent respiratory depression but rarely cause apnea. (Apnea is most common after rapid administration of large IV doses to patients who are chronically ill, elderly, or receiving concomitant narcotics.) When used for extended periods, benzodiazepines have been closely associated with the generation of delirium.

The highly lipid-soluble benzodiazepines (e.g., midazolam, diazepam) accumulate in fat after repeated or prolonged use, resulting in delayed recovery. The avid protein binding of benzodiazepines leads to frequent interactions with other protein-bound drugs and exposes hypoproteinemic patients to high concentrations of free (active) drug. Most benzodiazepines require hepatic metabolism and/or excretion; therefore, liver disease can prolong the action of these drugs (lorazepam and oxazepam are least subject to this effect). Conversely, patients with induced liver enzymes (e.g., alcoholics, barbiturate users) may require enormous doses for effect. Currently, all the commonly used benzodiazepines are inexpensive and compared priced based on hourly use. The properties of the three most frequently used parenteral benzodiazepines are contrasted in Table 17-4.

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**Table 17-3.**

<table>
<thead>
<tr>
<th>Nonopiates (Route)</th>
<th>Onset</th>
<th>Elimination Half-life</th>
<th>Metabolic Pathway</th>
<th>Active Metabolites</th>
<th>Dosing</th>
<th>Side Effects and Other Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine (IV)</td>
<td>30-40 s</td>
<td>2-3 h</td>
<td>N-demethylation</td>
<td>Norketamine</td>
<td>Loading dose 0.1-0.5 mg/kg IV followed by 0.05-0.4 mg/kg/h</td>
<td>Attenuates the development of acute tolerance to opioids. May cause hallucinations and other psychological disturbances.</td>
</tr>
<tr>
<td>Acetaminophen (PO)</td>
<td>30-60 min/variable</td>
<td>2-4 h</td>
<td>Glucuronidation, sulfonation</td>
<td>None</td>
<td>325-1,000 mg every 4-6 h; max dose ≤4 g/d</td>
<td>May be contraindicated in patients with significant hepatic dysfunction.</td>
</tr>
<tr>
<td>Acetaminophen (IV)</td>
<td>5-10 min</td>
<td>2 h</td>
<td>Glucuronidation, sulfonation</td>
<td>None</td>
<td>650 mg IV every 4 h—1,000 mg IV every 6 h; max dose ≤4 g/d</td>
<td></td>
</tr>
<tr>
<td>Ketorolac&lt;sup&gt;a&lt;/sup&gt; (IM/IV)</td>
<td>10 min</td>
<td>2.4-8.6 h</td>
<td>Hydroxylation, conjugation/renal excretion</td>
<td>None</td>
<td>30 mg IM/IV, then 15-30 mg IM/IV every 6 h up to 5 days; max dose = 120 mg/d × 5 days</td>
<td>Avoid nonsteroidal anti-inflammatory drugs in following conditions: renal dysfunction; GI bleeding; platelet abnormality; concomitant angiotensin converting enzyme inhibitor therapy, congestive heart failure, cirrhosis, asthma. Contraindicated for the treatment of perioperative pain in coronary artery bypass graft surgery.</td>
</tr>
<tr>
<td>Ibuprofen (IV)</td>
<td>N/A</td>
<td>2.2-2.4 h</td>
<td>Oxidation</td>
<td>None</td>
<td>400-800 mg IV every 6 h infused over &gt;30 min; max</td>
<td>Avoid nonsteroidal anti-inflammatory drugs in following conditions: renal dysfunction; GI bleeding; platelet abnormality: concomitant angiotensin converting enzyme inhibition.</td>
</tr>
</tbody>
</table>

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<sup>a</sup> Ketorolac is the only NSAID approved for IV use in the US. Ketorolac is associated with a higher risk of gastrointestinal bleeding compared to oral NSAIDs.

---
consciousness persists) that may be maintained using similar hourly doses. With short-term use, propofol has a rapid onset and offset of action; thus, it is particularly useful for

Propofol is an emulsion of an alkylphenol sedative with egg and soybean oil. Initial doses of 1 to 2 mg/kg IV result in profound, easily titrated sedation (but not analgesia if

Benzodiazepine Antagonism

Flumazenil is a competitive receptor antagonist capable of reversing the respiratory and central depressant effects of benzodiazepines in most patients. Chronic or high-dose

Flumazenil is a competitive receptor antagonist capable of reversing the respiratory and central depressant effects of benzodiazepines in most patients. Chronic or high-dose

Midazolam is a relatively long-acting sedative-annestic-anxiolytic agent available in oral or parenteral forms. Unpredictable absorption from the muscle usually limits use to the IV

Because of its lesser lipid solubility, smaller volume of distribution, and high gamma-aminobutyric acid (GABA) receptor affinity, lorazepam may have slower onset and longer

Diazepam is a relatively long-acting sedative-annestic-anxiolytic agent available in oral or parenteral forms. Unpredictable absorption from the muscle usually limits use to the IV

Midazolam is a potent (initially) short-acting benzodiazepine. High lipid solubility and the ability to cross the blood-brain barrier produce a rapid onset and prolonged action of diazepam. Doses of 2 to 10 mg (0.04 to 0.2 mg/kg IV) given every 5 to 10 minutes are reasonable to initiate therapy. Diazepam infusion contains the preservative propylene glycol, and use of high doses for long periods of time therefore can cause hyperosmolarity and metabolic acidosis. Because of its lesser lipid solubility, smaller volume of distribution, and high gamma-aminobutyric acid (GABA) receptor affinity, lorazepam may have slower onset and longer

Diazepam is a relatively long-acting sedative-annestic-anxiolytic agent available in oral or parenteral forms. Unpredictable absorption from the muscle usually limits use to the IV

Table 17-4. Comparison of the Properties of Parenteral Benzodiazepines

<table>
<thead>
<tr>
<th>Compound</th>
<th>Duration of Action</th>
<th>Hepatic Metabolism Required?</th>
<th>Metabolites Active?</th>
<th>Relative Hourly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>Long</td>
<td>Yes</td>
<td>Yes</td>
<td>$</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Long</td>
<td>No</td>
<td>No</td>
<td>$</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Variable</td>
<td>Yes</td>
<td>Yes</td>
<td>$</td>
</tr>
</tbody>
</table>

Diazepam is a relatively long-acting sedative-annestic-anxiolytic agent available in oral or parenteral forms. Unpredictable absorption from the muscle usually limits use to the IV

If the ICU. Flumazenil should be used cautiously because it may precipitate withdrawal (agitation, vomiting, and seizures), especially among chronic benzodiazepine users. For patients with suspected combined (benzodiazepine and tricyclic antidepressants) drug overdose, flumazenil can precipitate seizures, presumably as a result of unmasking tricyclic effects.

Propofol

Propofol is an emulsion of an alkylphenol sedative with egg and soybean oil. Initial doses of 1 to 2 mg/kg IV result in profound, easily titrated sedation (but not analgesia if consciousness persists) that may be maintained using similar hourly doses. With short-term use, propofol has a rapid onset and offset of action; thus, it is particularly useful for

For patients > 65 y or < 50 kg, 15 mg IV/IM every 6 h to a maximum dose of 60 mg/d for 5 days.

IM, intramuscular; max, maximum; N/A, not applicable; PO, orally; PR, rectally.

Reproduced from Barr J, Fraser GL, Puntilllo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care

1 mg total) are customary. Although flumazenil may confirm a diagnosis of benzodiazepine overdose, it rarely alters patient management significantly and, thus, is seldom needed in the ICU. Flumazenil should be used cautiously because it may precipitate withdrawal (agitation, vomiting, and seizures), especially among chronic benzodiazepine users. For patients with suspected combined (benzodiazepine and tricyclic antidepressants) drug overdose, flumazenil can precipitate seizures, presumably as a result of unmasking tricyclic effects.

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patients who require repeated neurological assessment. Similar to other highly lipid-soluble agents, long-term administration can lead to saturation of fatty tissue and prolonged recovery times. Because propofol is conjugated in the liver to inactive metabolites, which are renally excreted, it is a good choice for patients with multiple organ failure. Despite these advantages, propofol has clear limitations. Potent cardiovascular depression causes hypotension in up to one third of patients, especially when loading doses are used. Because of its fat content, the vehicle provides 1.1 cal/mL and can cause hypertriglyceridemia and (very rarely) hyperepidemic pancreatitis. For unclear reasons, a very small minority of patients develop a potentially lethal syndrome of metabolic acidosis and multiple organ failure termed as the propofol infusion syndrome (see Chapter 33). The vehicle may cause allergic reactions, and users should not be surprised by green-tinged urine produced by excretion of the phenol metabolites. Propofol is most commonly used in patients receiving mechanical ventilation where this therapy is titrated to the lowest effective dose. In general, propofol is not employed unless either the patient is intubated or the drug is administered by a qualified and vigilant team for a bedside procedure. This limitation requires transition to an alternative sedating agent after the patient is extubated.

**Dexmedetomidine**

Dexmedetomidine is a centrally acting α₂ agonist that produces effective sedation but not analgesia. The drug has gained popularity because it has relatively little effect on respiratory drive or alertness and has a short onset of action and brief half-life, allowing easy titration. In addition, dexmedetomidine may be continued during and after extubation, which allows sedation to be maintained and tapered as tolerated. Dexmedetomidine has many of the same desirable properties as propofol with much less consciousness impairment. This agent may decrease opioid requirements and seems particularly effective in managing withdrawal syndromes and difficult ventilator weaning. Unfortunately, loading doses cause bradycardia and hypotension in many patients and the drug can induce apnea. However, given the benefit profile above, dexmedetomidine is a useful sedative agent for managing agitated and combative patients during mechanical ventilation and during the progression toward extubation.

**Etomidate**

Etomidate is an imidazole sedative-hypnotic that lacks analgesic properties. Because etomidate rarely causes hypotension and has both rapid onset (seconds) and brief duration of action (5 minutes), it is a popular choice for brief procedures and for intubation. A dose of 0.3 mg/kg is customary, but a wide therapeutic margin exists. Even though the sedative effect of etomidate lasts only minutes, the imidazole structure of the compound is capable of inhibiting adrenal glucocorticoid synthesis for a day. The clinical importance of this biochemical observation is unclear for a single dose, but long-term etomidate administration has been associated with higher mortality rates. One practical implication of the glucocorticoid-suppressing effect is that adrenal function (ACTH) testing after etomidate use may lead to the conclusion that the patient has at least “relative” adrenal insufficiency. This finding could prompt exogenous, almost certainly unnecessary, glucocorticoid administration by the physician unfamiliar with this phenomenon. Given the undeniable advantages of etomidate for short-term use and the uncertainties of long-term safety, etomidate use should probably be restricted to one or two doses in any given patient. Historically, benzodiazepines and propofol have been commonly used to sedate ICU patients. Recent sedation practice in adults continues to emphasize midazolam and propofol in ICU sedation. There has been decreasing lorazepam use, noticeably increased use of ketamine, and rare administration of barbiturates or diazepam. Dexmedetomidine is now more commonly administered for ICU sedation. Clinical pharmacology of sedatives typically prescribed for ICU patients is summarized in Table 17-5. Titration sedation may be accomplished with tools such as the RASS (Table 17-6).

### Table 17-5.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Onset After IV Loading Dose</th>
<th>Elimination Half-life</th>
<th>Active Metabolites</th>
<th>Loading Dose (IV)</th>
<th>Maintenance Dosing (IV)</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>2-5 min</td>
<td>3-11 h</td>
<td>Yes</td>
<td>0.01-0.05 mg/kg over several minutes</td>
<td>0.02-0.1 mg/kg/h</td>
<td>Respiratory depression, hypotension</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>15-20 min</td>
<td>8-15 h</td>
<td>None</td>
<td>0.02-0.04 mg/kg (≤2 mg)</td>
<td>0.02-0.08 mg/kg (≤10 mg/kg)</td>
<td>Respiratory depression, hypotension; propylene glycol-related acidosis, nephrotoxicity</td>
</tr>
<tr>
<td>Diazepam</td>
<td>2-5 min</td>
<td>20-120 h</td>
<td>Yes²</td>
<td>5-10 mg</td>
<td>0.03-0.1 mg/kg (≤2 mg/h)</td>
<td>Respiratory depression, hypotension, phlebitis²</td>
</tr>
<tr>
<td>Propofol</td>
<td>1-2 min</td>
<td>Short-term use = 5-12 h Long-term use = 50-186 h</td>
<td>None</td>
<td>5 μg/kg/min over 5 min²</td>
<td>5-50 μg/kg/min</td>
<td>Pain on injection;³ hypotension, respiratory depression, hypertriglyceridemia, pancreatitis, allergic reactions, propofol-related infusion syndrome; deep sedation with propofol is associated with significantly longer emergence times than with light sedation</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>5-10 min</td>
<td>1.8-3.1 h</td>
<td>None</td>
<td>1 μg/kg over 10 min²</td>
<td>0.2-0.7 μg/kg/h²</td>
<td>Bradycardia, hypotension; hypotension with loading dose; loss of airway reflexes</td>
</tr>
</tbody>
</table>

²Active metabolites prolong sedation, especially in patients with renal failure.
³Administer IV loading dose of propofol only in those patients in whom hypotension is unlikely to occur.
⁴Avoid IV loading doses of dexmedetomidine in hemodynamically unstable patients.
⁵Dexmedetomidine maintenance infusion rate may be increased to 1.5 μg/kg/h as tolerated.
Phlebitis occurs when diazepam is injected into peripheral veins.

Pain at the injection site occurs commonly when propofol is administered through peripheral veins.


### Table 17-6.

**Richmond Agitation and Sedation Scale (RASS)**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combative (score of 4)</td>
<td>Overtly combative, violent, immediate danger to staff</td>
</tr>
<tr>
<td>Very Agitated (score of 3)</td>
<td>Pulls or removes tubes or catheters, aggressive</td>
</tr>
<tr>
<td>Agitated (score of 2)</td>
<td>Frequent nonpurposeful movement, fights ventilator</td>
</tr>
<tr>
<td>Restless (score of 1)</td>
<td>Anxious but movements not aggressive or vigorous</td>
</tr>
<tr>
<td>Alert and calm (score of 0)</td>
<td>Alert and calm</td>
</tr>
<tr>
<td>Drowsy (score of -1)</td>
<td>Not fully alert but has sustained awakening (eye opening or eye contact) to voice (≥10 s)</td>
</tr>
<tr>
<td>Light sedation (score of -2)</td>
<td>Briefly awakens with eye contact to voice (&lt;10 s)</td>
</tr>
<tr>
<td>Moderate sedation (score of -3)</td>
<td>Movement or eye opening to voice but no eye contact</td>
</tr>
<tr>
<td>Deep sedation (score of -4)</td>
<td>No response to voice but movement or eye opening to physical stimulation</td>
</tr>
<tr>
<td>Cannot be aroused (score of -5)</td>
<td>No response to voice or physical stimulation</td>
</tr>
</tbody>
</table>


### Neuroleptics/Antipsychotics

**Haloperidol**

Haloperidol, a butyrophenone, has become popular for control of severely agitated patients in the ICU, particularly when delirium is evident. Initial IV doses of 1 to 2 mg commonly are doubled every 15 to 30 minutes until behavioral control is obtained. (Some clinicians begin with larger doses of 5 to 10 mg, when initial agitation is violent.) Afterward, a recurring dose of 2 to 5 mg every 6 to 8 hours is often sufficient to render a calm, awake patient. For severely agitated patients, the combination of a benzodiazepine and haloperidol is superior to either agent alone. The efficacy of haloperidol is inconsistent and its actions are somewhat delayed. For these reasons, it is not ideal for immediate intervention in a combative patient, although it is frequently used in this way. It has a large volume of distribution and half-life approaching a day in patients with normal hepatic function. Haloperidol may lower the seizure threshold, extend the QT interval, and (rarely) precipitate **torsades de pointes**, neuroleptic malignant syndrome, transient extrapyramidal reactions, and tardive dyskinesia. Extrapyramidal effects of IV haloperidol appear to be less common than with oral use.

**Olanzapine/Quetiapine**

Olanzapine is an atypical antipsychotic that has also been used to treat agitated delirium in the ICU. It may also be helpful in situations where prolonged sedation is required. Relatively little data exist on the use of this drug among critically ill patients. It is available for intramuscular and sublingual as well as enteral use. Although olanzapine can cause tardive dyskinesia and neuroleptic malignant syndrome, QT prolongation, and cardiac arrhythmias, these are rarely reported. Quetiapine is a class II antipsychotic, which may also be given for prolonged sedation in the critical care setting. It is more somnolence-inducing than olanzapine, and QT prolongation with this drug is somewhat more likely than with olanzapine. Though rare, extrapyramidal symptoms and neuroleptic malignant syndrome have been reported with the use of this drug. One obvious advantage with either olanzapine or quetiapine is the opportunity to continue them after resolution of the critical phase of illness. Dose modification is required for both in the setting of liver disease. Although not commonly used, risperidone provides another antipsychotic alternative with calming properties that may be occasionally useful.

Antipsychotic agents are generally not recommended as a delirium prevention strategy. Although data are limited, administration of antipsychotic agents is endorsed by many critical care specialists for the management of delirious patients (see below). There are limited trial data verifying the safety and efficacy of haloperidol for the treatment of delirium in adult ICU patients. Data on the use of other antipsychotics in this patient population are also limited. **Table 17-7** summarizes pharmacologic data on antipsychotics available for use in ICU patients.

### Table 17-7.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Ziprasidone</th>
<th>Haldol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>***</td>
<td>**</td>
<td>*</td>
<td>**</td>
<td>****</td>
</tr>
<tr>
<td>Serotonin</td>
<td>***</td>
<td>***</td>
<td>*</td>
<td>****</td>
<td>**</td>
</tr>
<tr>
<td>Alpha- adrenergic</td>
<td>**</td>
<td>*</td>
<td>***</td>
<td>*</td>
<td>0</td>
</tr>
</tbody>
</table>
Histamine

Muscarinic

Dose 0.25-0.5 mg p.o. b.i.d. 2.5-5 mg/d 12.5-25 mg p.o. q8-12h 20-40 mg p.o. b.i.d.; 10 mg IM 2-4 mg; cut dose to 1-2 mg for elderly

Time to peak 1 h 5-6 h 1 h 5 h 2-6 h

Half-life 3-24 h 20-70 h 7 h 4-10 h 18 h

Comments Not studied in ICU patients 40% by 1st-pass metabolism Hold TFs for 30 minutes Absorption doubled with food Prolongation of QTs (doses of >50 mg/d)

Sedation ** *** *** ** *

EPS *** *** * * **

NMS * * * * *

Anticholinergic * *** ** *

Orthostasis **** *** ** ** 0

Hyperglycemia * *** ** *

QTc prolongation * ? * *** ***

Seizure 0.3% incidence 0.9% incidence 0.05%-0.5% incidence 0.4% incidence Rare, lowers seizure threshold

Increasing strength of effect

Courtesy of Kim Cartie, PharmD, BCCCP

TFs, Tube feedings.

Neuromuscular Blocking Agents

Mechanism of Action

Normally, electrical impulses reach the neuromuscular junction, causing calcium-mediated release of acetylcholine into the junctional cleft. Acetylcholine binding to nicotinic muscle receptors then causes a sodium-potassium flux (depolarization). Through a combination of acetylcholine reuptake and local degradation by “true or specific” acetylcholinesterase, muscle repolarization occurs and the opportunity for subsequent contraction is restored. A second nonspecific plasma enzyme, pseudocholinesterase, metabolizes acetylcholine and acetylcholine-like molecules. Depolarizing neuromuscular blockers stereochemically resemble acetylcholine and mimic its action at the neuromuscular junction resulting in Na⁺–K⁺ flux across the muscle. Depolarizing blockers are not metabolized in the neuromuscular junction by acetylcholinesterase; therefore, persistent depolarization occurs until the neuromuscular blocker diffuses out of the synaptic cleft, where it is metabolized by plasma or pseudocholinesterase. Nondepolarizing blockers act by passively occupying acetylcholine binding sites or sodium-potassium ion channels, thereby competitively blocking the depolarizing action of acetylcholine.

Indications

With the exception of endotracheal intubation and early stage management of ARDS, neuromuscular blockade is seldom needed in the ICU when adequate sedation is provided; yet, carefully selected patients clearly benefit. Unless absolutely necessary to preserve life, awake neuromuscular blockade is never an acceptable alternative to sedation.

Experience with these inherently dangerous agents should come from carefully supervised use and cannot be learned safely by only reading about them. Because of the potential for numerous complications, neuromuscular blocking agents (NMBA) should be used in the lowest possible doses, for the shortest possible time, and only after sedation alone has proven inadequate to accomplish distinct therapeutic objectives.

Commonly accepted indications for neuromuscular blockade are given in Table 17-8. Facilitation of endotracheal intubation is the most common indication, and termination of breathing effort is routinely needed for the safe intubation of agitated and hypoxemic patients, especially when difficulty is anticipated. Extreme caution is indicated, however; as a rule, the hazards of neuromuscular blockade-induced paralysis for intubation parallel the perceived need for muscle relaxation. For example, use of neuromuscular blockers in morbidly obese patients or those with spinal instability can precipitate complete upper airway obstruction. Ideally, expert backup and provisions to secure the airway supported by endoscopic visualization and surgical intervention if necessary should be available when using NMBA.

Diseases in which muscular contraction is itself harmful (e.g., tetanus and hemodynamic instability resulting from status epilepticus) often benefit from neuromuscular blockade. NMBA may be instrumental in the first days of severe ARDS, with at least one influential clinical trial reporting a mortality benefit with their use. It is important to remember that although NMBA terminate the muscular convulsive activity, they do nothing to terminate any chaotic cerebral electrical activity damaging the brain. Because neuromuscular blockers obscure clinical assessment of seizure (convulsive) activity, it is best if continuous electroencephalographic monitoring is provided when seizing patients are chemically paralyzed.

<table>
<thead>
<tr>
<th>Table 17-8. Potential Indications for Neuromuscular Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotracheal intubation</td>
</tr>
<tr>
<td>Muscle relaxation during surgery</td>
</tr>
</tbody>
</table>

P.366
Facilitation of mechanical ventilation or oxygenation refractory to deep sedation
Prevention of strong effort and excessive lung stretch
Reduction of oxygen consumption
Injury prevention (e.g., electroconvulsive therapy)
Termination of tetanus/convulsive activity
Prevention of intracranial hypertension

High levels of positive end-expiratory pressure (PEEP) and modes of ventilation with prolonged inspiratory times (e.g., extended ratio or airway pressure release ventilation) are sometimes actively opposed by patients. Lung-protective, low tidal volume ventilation and "permissive hypercapnia" also increase ventilatory drive. In these settings, sedation alone is often sufficient to provide comfort, aid ventilation, and lower peak airway pressures. Neuromuscular blockers, however, are sometimes necessary to facilitate synchronous ventilation or to restrain dysfunctional efforts, especially when respiratory drive is very high (e.g., severe metabolic acidosis). Chemical paralysis also can reduce oxygen consumption in patients with marginal oxygenation, but there is little evidence that neuromuscular blockade is superior to deep sedation in this situation for the same level of ventilation. When sedation is optimally managed, the need to sustain neuromuscular blockade to facilitate mechanical ventilation is relatively uncommon.

Cautions
Neuromuscular blockade poses many dangers: ranking behind loss of the airway and inappropriately enforced reduction of ventilating frequency and minute ventilation, the most frightening may be the potential for the awake patient to receive chemical paralysis. Insufficient sedation is difficult to recognize: hypertension, tachycardia, diaphoresis, and lacrimation are the only possible physiologic manifestations. Hopes that BIS monitoring would eliminate awareness during neuromuscular blockade have not been realized.

Table 17-9. Conditions Influencing the Intensity of Neuromuscular Blockade

<table>
<thead>
<tr>
<th>Conditions That Potentiate Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidosis</td>
</tr>
<tr>
<td>Hypocalcemia</td>
</tr>
<tr>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Hypermagnesemia</td>
</tr>
<tr>
<td>Hypoanæmia</td>
</tr>
<tr>
<td>Hypothermia</td>
</tr>
<tr>
<td>Neuromuscular diseases</td>
</tr>
<tr>
<td>Guillain-Barre syndrome</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis, polio</td>
</tr>
<tr>
<td>Drug interactions</td>
</tr>
<tr>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>β-Blockers</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>Clindamycin</td>
</tr>
<tr>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Procarbamide</td>
</tr>
<tr>
<td>Quinidine</td>
</tr>
<tr>
<td>Tetracycline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditions That Inhibit Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkalosis</td>
</tr>
<tr>
<td>Burns</td>
</tr>
<tr>
<td>Prolonged paralytic use</td>
</tr>
</tbody>
</table>

Short-term use in the operating room; therefore, actions, interactions, and side effects for critically ill patients in the ICU after long-term administration are less predictable.

The terms critical illness polyneuropathy and myoneuropathy have been coined to describe the residual weakness observed in some ICU patients, typically after prolonged administration of neuromuscular blockers in conjunction with glucocorticoids. Profound, prolonged weakness can develop as a result of critical illness itself, however, this syndrome is probably more common following continuous long-term use of neuromuscular blockers, especially when steroids are administered simultaneously. Some cases of myopathy or neuromyopathy are associated with elevation of creatine phosphokinase (CPK) or aldolase levels; however, normal levels of these compounds do not preclude the syndrome. The specific neuromuscular blocker used, the total dose employed for muscle relaxation, the duration of therapy, the presence of renal failure, and the quantity and duration of corticosteroids all may be risk factors for the development of this syndrome. Unfortunately, there are little convincing data to indicate that selecting one agent over another or monitoring the depth of neuromuscular blockade decreases the risk. Avoidance of corticosteroids is beneficial.

The potency and duration of paralytic agents are affected by the duration of therapy and by the presence of concomitant medications and medical conditions. Burns and use of methylxanthines, phenytoin, lithium, corticosteroids, and carbamazepine all reduce the effectiveness of NMBA (Table 17-9). Edematous states produce more complex problems: by increasing the volume of distribution, edema makes initial drug-induced paralysis more difficult to achieve; however, the large reservoir of drug that accumulates in edema fluid may prolong recovery. Tachyphylaxis is sometimes a consequence of long-term use.

Respiratory acidosis and metabolic alkalosis, hypokalemia, hyperkalemia, hypercalcemia, hypermagnesemia, and hypothermia all potentiate neuromuscular blockade. Patients with "derivation hypersensitivity" caused by diseases such as myasthenia gravis and Guillain-Barré syndrome are particularly sensitive to depolarizing paralytic agents. β-Blockers, calcium channel blockers, cyclosporine, aminoglycosides, tetracycline, clindamycin, and the antiarrhythmics procainamide and quinidine also amplify neuromuscular blockade.
Specific Blockers

Depolarizing Neuromuscular Blockers

Succinylcholine is the drug of choice for many intubations because it has a very rapid onset of action (seconds) and a brief duration (<10 minutes). Because it is degraded rapidly by plasma cholinesterase, most of the administered dose never reaches the neuromuscular junction. Succinylcholine causes fasciculations (depolarization) in the skeletal muscle but does not affect smooth muscle action. Despite its brief duration of action, succinylcholine is not without side effects. Most adult patients develop a sympathomimetic response; however, hypotension may occur when succinylcholine is combined with propofol. Succinylcholine is not suited for repeated injection or constant infusion because when given in this manner, it causes vago nerve stimulation and bradycardia. If more than one dose of succinylcholine is required, atropine should be given before the second dose.

Depolarization causes muscle contraction and, hence, potassium release from muscles. Plasma potassium increases of 0.5 to 1 mEq/L are common; but among patients with peritonitis, burns, multiple trauma, or rhabdomyolysis, hyperkalemia may be severe. Patients with increased numbers of acetylcholine receptors because of denervation or infections may be more sensitive to succinylcholine. Vomiting caused by abdominal muscle contraction and postparalysis muscle pain may result from succinylcholine use but may be attenuated by pretreatment with a subparalyzing dose (10% to 15% of the usual dose) of a nondepolarizing blocker. Succinylcholine raises intraocular pressure and should be avoided in patients with glaucoma or ocular injuries.

Nondepolarizing Neuromuscular Blockers

Nondepolarizing neuromuscular blockers act by preventing the action of acetylcholine at its receptor. Nondepolarizing blockers may be grouped conveniently by several basic properties: duration of action, route of metabolism and excretion, propensity to release histamine, and the tendency to cause vagal blockade (Table 17-10). Many of these compounds (e.g., pancuronium, vecuronium, rocuronium, pipecuronium) chemically resemble corticosteroids. Each of the nondepolarizing blockers has a slower onset of action than succinylcholine but produces neuromuscular blockade longer than succinylcholine. Duration of action ranges from 20 minutes for mivacurium to often more than an hour for pancuronium, pancuronium, doxacurium, metocurine, and tubocurarine.

Pancuronium is the longest acting of the nondepolarizing agents but falls short of being the perfect drug for neuromuscular blockade in the ICU because it requires renal excretion like tubocurarine, metocurine, doxacurium, and pipecuronium. Pancuronium also undergoes substantial (approx. 20%) hepatic metabolism yielding active metabolites complicating its use in hepatic failure. Pancuronium also has modest histamine-releasing properties and vagolytic effects that may cause tachycardia and hypotension.

Vecuronium is used widely because of its quick onset, intermediate duration of action, and paucity of cardiovascular effects. Because vecuronium is cleared in large part (approx. 80%) by hepatic metabolism and biliary excretion, it is a less than ideal choice for patients with liver disease. Although not cleared directly by the kidney, vecuronium has active metabolites that are renally cleared. Hence, reports of prolonged neuromuscular blockade after vecuronium administration in patients with renal insufficiency are not surprising.

Atracurium, cisatracurium, and mivacurium have theoretical advantages for patients with hepatic or renal insufficiency because these drugs undergo extensive plasma degradation. Mivacurium is broken down by pseudocholinesterase, whereas atracurium undergoes esterase degradation and spontaneous breakdown at physiologic pH and temperature termed “Hofmann elimination.” Because of its metabolism, atracurium is probably least affected by the presence of renal failure but is influenced by hypothermia and acidosis. Metabolism of atracurium yields laudanosine, an excitatory amine cleared by the kidney that may precipitate seizures. Breakdown of atracurium is delayed by hypoalbuminemia and acidosis, but unlike most other neuromuscular blockers, duration of effect is not increased by advanced age. Cisatracurium may result in lesser laudanosine generation.

General Recommendations: Intubation

Rapidity of onset and brief duration of action make succinylcholine the drug of choice for most ICU intubations, unless neuromuscular diseases, burns, or electrolyte disorders dictate otherwise. Nondepolarizing properties of mivacurium along with short duration of action and plasma metabolism make it a second-line choice for patients with contraindications to succinylcholine. Rocuronium is another acceptable alternative.

Long-acting, nondepolarizing neuromuscular blockers may be used as well. The onset of paralysis is hastened by administration of low doses or subparalytic “priming doses” given several minutes before the paralytic dose. Vecuronium and mivacurium represent good alternate choices for rapid sequence intubation because both drugs exhibit a priming effect and have an intermediate duration of action, and even large doses of both agents have minimal side effects. Although atracurium and vecuronium can be used for intubation, their longer duration of action can be problematic if the airway cannot be cannulated.

Table 17-10. Properties of Neuromuscular Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose (mg/kg)</th>
<th>Onset (min)</th>
<th>Duration</th>
<th>Histamine Release</th>
<th>Vagal Blockade</th>
<th>Metabolism</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium</td>
<td>0.4-0.6</td>
<td>2-3</td>
<td>Intermediate</td>
<td>+</td>
<td>0</td>
<td>Mostly nonenzymatic</td>
<td>Renal metabolite excretion</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>0.15-0.2</td>
<td>3-6</td>
<td>Intermediate</td>
<td>&lt;Atracurium</td>
<td>0</td>
<td>Mostly nonenzymatic</td>
<td>Renal metabolite excretion</td>
</tr>
<tr>
<td>Doxacurium</td>
<td>0.025-0.08</td>
<td>3-5</td>
<td>Long</td>
<td>0</td>
<td>0</td>
<td>Minimal</td>
<td>Renal</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>0.15</td>
<td>2-3</td>
<td>Short</td>
<td>In large doses</td>
<td>0</td>
<td>Extensive in plasma</td>
<td>Minimal</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>0.06-0.1</td>
<td>1-3</td>
<td>Long</td>
<td>0 to +</td>
<td>+</td>
<td>Moderate</td>
<td>Renal &gt;&gt; hepatic</td>
</tr>
</tbody>
</table>
Sustained Neuromuscular Blockade

A role for prolonged neuromuscular blockade is seen early in the course of acute respiratory distress syndrome for patients with critical hypoxemia and in other life-threatening conditions associated with hypoxemia, respiratory acidosis, or hemodynamic compromise. Neuromuscular blockade may also be used for extended periods to manage overt shivering in therapeutic hypothermia. For patients with reasonable hemodynamic reserves and near-normal hepatic and renal function, paralysis for longer than 1 hour can be accomplished safely and economically with pancuronium. Patients with tenuous hemodynamic status may be less likely to experience adverse cardiovascular effects if paralyzed with vecuronium, atracurium, or cisatracurium. Hepatic insufficiency is an additional consideration favoring atracurium or cisatracurium. Renal insufficiency favors using vecuronium.

Doxacurium, pipercuronium, and vecuronium do not offer any substantial advantage over pancuronium with respect to cost, duration of action, side effects, or elimination profiles. Despite the limitations of pancuronium, it can be used safely even for patients with advanced hepatic and renal insufficiency if care is taken to avoid overdose through close clinical monitoring.

Patients with prolonged neuromuscular blockade are at risk for a variety of complications. Optimal care for these patients includes scheduled eye care including use of lubricated drops or assured eyelid closure, because of the risk of corneal injury. Despite presumed reduction of metabolic demands associated with neuromuscular blockade, nutritional needs must be addressed. Controversy exists whether enteral or parenteral feeding is appropriate in these patients. If patients respond appropriately to a gut stimulation program, enteral feeding is preferred. As already noted, these patients are at increased risk for complications of immobility and require careful screening for skin protection, secretion clearance, and bedside physical therapy for deconditioning and contractures.

Complications of Neuromuscular Blockade

Pseudocholinesterase Deficiency and Sustained Blockade

Pseudocholinesterase is the plasma enzyme that metabolizes acetylcholine, succinylcholine, and mivacurium. Genetic or acquired reductions in this enzyme increase the duration of neuromuscular blockade when using these drugs. Up to 5% of patients are heterozygous for plasma cholinesterase, resulting in prolongation of neuromuscular blockade by several minutes. Approximately, 1 in 3,000 persons has a homozygous pseudocholinesterase deficiency, extending the duration of the neuromuscular blockade to 6 to 8 hours. Because the goal of therapy in the ICU, unlike the operating room, is usually to produce muscle relaxation that lasts for hours, prolonged drug effect is usually of less consequence. There is no certain clue to pseudocholinesterase deficiency other than a clear history of prior prolonged paralysis; however, cholinesterase levels tend to decrease in patients with liver disease, renal failure, advanced age, pregnancy, marked anemia, and organophosphate toxicity.

Malignant Hyperthermia

Malignant hyperthermia is a calcium channel-mediated genetic disorder that is rarely precipitated by use of neuromuscular blockers, but when it occurs, it is usually in combination with an inhalational anesthetic (see Chapter 28). Clinical features include the rapid development of muscular rigidity, high fever, and enormous increases in metabolic rate resulting in metabolic acidosis and massive increases in CO₂ production and O₂ consumption. If left untreated, cardiac ischemia and ventricular arrhythmias occur commonly. Treatment consists of removing the offending agent(s) and administering IV dantrolene.

Assessing Depth of Neuromuscular Blockade

Approximately, 50% receptor blockade is required to cause some muscle weakness, with 95% blockade needed for complete muscular relaxation. Interestingly, the diaphragm is one of the muscles most resistant to neuromuscular blockade, requiring 90% or more of receptors to be blocked to effect drug-induced paralysis. It can be difficult to clinically assess the degree of neuromuscular blockade in the ICU, but as a practical bedside test, the ability to sustain a head lift for several seconds indicates reversal of paralysis and is more reliable than tests of negative inspiratory force, vital capacity, tongue protrusion, or grip strength. Simply observing that the patient is overbreathing, the rate set on the ventilator indicates that drug-induced muscle relaxation is not complete.

A peripheral nerve stimulator (PNS) provides the objective index of the intensity of neuromuscular blockade. There is little definitive evidence to indicate improved outcomes with PNS compared to clinical evaluation, provided that the patient is otherwise not in nonpharmacologic coma. If employed, the goal of PNS use is to prevent complete obliteration of a "train of four" electrical stimulus. If patients are able to produce one to three muscular contractions per four electrical stimuli, overdosage of a neuromuscular blocker has not occurred. Unfortunately, appropriate monitoring sites can be difficult to find and maintain, and it is possible to have complete obliteration of the train of four stimulus, even with intact diaphragm function. The practical implications of this observation are that patients may exhibit ventilator dyssynchrony despite profound peripheral skeletal muscle blockade and desired obliteration of diaphragm function may require aggressive blockade of peripheral muscle function. A more commonly used monitoring strategy is to allow the potentially arousable patient to move before subsequent doses of a neuromuscular blocking agent are given. This practice has several practical advantages: (1) it does not require special equipment or training or induce patient discomfort; (2) it allows early discovery of patients who are inadequately sedated; (3) it permits physical assessment that may uncover new coincident conditions; and (4) it often reveals that continued neuromuscular blockade is not necessary, thereby reducing duration of drug effect and expense. Regardless of the method of minute-to-minute monitoring, it is prudent to interrupt the administration of neuromuscular blockade at least once each day to prevent inadvertent overdose.

Reversal of Neuromuscular Blockade

The reversing agents (e.g., neostigmine, pyridostigmine, and edrophonium) act by raising acetylcholine levels in the neuromuscular junction and, therefore, will not reverse the blockade of succinylcholine or the profound (ion channel) blockade because of nondepolarizing blockers. Active reversal of paralysis is rarely necessary in the ICU, and use of these agents risks muscarinic stimulation (bradycardia, bronchorrhea, and salivation). Muscarinic effects may be countered by pretreatment with the anticholinergic atropine or glycopyrrolate.

Delirium

The National Institutes of Health defines delirium as sudden severe confusion and rapid changes in brain function occurring with physical or mental illness. The most common feature of delirium is inattention. The pathophysiology of delirium as associated with critical illness remains largely uncharacterized and may vary depending on the cause. Although a variety of metabolic pathways have been proposed, these remain unproven, making pharmacologic management strategies empirical.

Regardless of the cause and underlying pathophysiology, delirium is a frequent and important event in critically ill patients. There is no diagnostic blood, electrophysiology, or imaging test for delirium, which, therefore, remains a clinical diagnosis. Estimates for the incidence of delirium in the ICU range from 16% to 89%, with reported incidence affected by both the characteristics of the ICU population studied and by the diagnostic criteria employed. Identified risk factors include advanced age and the presence of a condition associated with coma followed by treatment with sedation, a neurologic diagnosis, and increased severity of illness. Delirium is associated with increased mortality and decreased

<table>
<thead>
<tr>
<th>Drug</th>
<th>Blockade Duration</th>
<th>Reversal</th>
<th>Effects</th>
<th>Site of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancuronium</td>
<td>1-3</td>
<td>Long</td>
<td>0</td>
<td>Moderate</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>0.6</td>
<td>Intermediate</td>
<td>0</td>
<td>Moderate</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>1.0-1.5</td>
<td>Short</td>
<td>0</td>
<td>Extensive in plasma</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.08-0.10</td>
<td>Intermediate</td>
<td>0</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

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long-term cognitive functioning, but any causal connection remains uncertain.

There are two distinct forms of delirium, hypoactive and agitated (or hyperactive). When individual patients intermittently have both forms, it is termed “mixed delirium.” The hypoactive form is characterized by inattention, disordered thinking, and decreased level of consciousness without agitation. Pure agitated delirium affects less than 2% of patients with delirium in the ICU. Patients with hypoactive delirium are less likely to survive, but those who do survive may have better long-term function than those with agitated or mixed delirium. Currently, the evidence that specific treatment of delirium may improve outcomes is tenuous.

In routine practice, delirium is frequently unappreciated. Active screening identified delirium in up to 64% of patients who would be considered delirious by a psychiatrist, geriatrician, or neurologist. The most commonly used clinical scale for delirium assessment, the Confusion Assessment Method for the ICU (CAM-ICU), Table 17-11, evaluates the patient at a single time point. It is not clear if the use of a consistent scale is more sensitive than unstructured assessment by a trained bedside clinician prompted to look for delirium.

There is some evidence that delirium may be preventable. Outside the ICU, reorientation, noise reduction, cognitive stimulation, social interactions, vision and hearing aids, adequate hydration, and early mobilization may reduce the incidence of delirium in hospitalized patients. The role of antipsychotic agents as prophylaxis for reduced incidence and severity of delirium remains unclear. Sedation with dexmedetomidine rather than benzodiazepines may reduce the incidence of delirium in the ICU. Although most providers accept the proposal that dexmedetomidine leads to less frequent or less severe delirium than benzodiazepines, evidence on which this statement is made is tenuous.

Table 17-11. Diagnosis of Delirium in Critically Ill Patients (CAM-ICU)

<table>
<thead>
<tr>
<th>System, Scoring Method, and Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confusion Assessment Method for the ICU (CAM-ICU)</strong></td>
</tr>
<tr>
<td>Scoring is positive or negative according to the presence or absence of criteria listed</td>
</tr>
<tr>
<td>Patient must be sufficiently awake (RASS score -3 or more) for assessment according to the following criteria:</td>
</tr>
<tr>
<td>• An acute change from mental status at baseline or fluctuating mental status during the past 24 h (must be true to be positive)</td>
</tr>
<tr>
<td>• More than 2 errors on a 10-point test of attention to voice or pictures (must be true to be positive)</td>
</tr>
<tr>
<td>• If the RASS is not 0 and the above two criteria are positive, the patient is delirious</td>
</tr>
<tr>
<td>• If the RASS is 0 and the above two criteria are positive, test for disorganized thinking using 4 yes/no questions and a 2-step command: ≥1 error means the patient is delirious; ≤1 error excludes delirium</td>
</tr>
<tr>
<td>RASS, Richmond Agitation and Sedation Scale.</td>
</tr>
</tbody>
</table>


Limited trial data support efficacy of a drug treatment protocol for established delirium in patients in the ICU. In a small study, delirium resolved faster in patients receiving quetiapine, and the use of this agent increased the number of individuals discharged to their own home or rehabilitation. Because delirium is a clinical diagnosis, however, devising rigorous trial design among comparable patient populations is problematic.

Accumulating evidence does suggest that management of sedation and delirium can have an important effect on the outcome of patients treated in the ICU. Available data suggest that best outcomes are achieved with the use of a protocol in which depth of sedation and the presence of pain and delirium are routinely evaluated, pain is treated promptly, administration of sedation is minimized, and early mobilization is accomplished when possible.

**SUGGESTED READINGS**


Chapter 18
General Supportive Care

• Key Points

1. Failure to systematically review the available database relevant to prior history, events immediately preceding presentation, vital organ performance, and therapy prescribed before and during hospitalization promotes misinterpretation, inappropriate care plans, or ineffective communications among caregivers that translate into adverse outcomes or protracted hospital stays.

2. Although the intensive care unit (ICU) practitioner must intercede quickly and decisively when action is needed to avert disaster, in most circumstances, the clinician’s prime objective should not be to reestablish “normal physiology” as quickly as possible but rather to encourage smooth resolution or adaptation to the pathophysiologic insult.

3. In the presence of uncertainty, conducting a closely observed “therapeutic minitrial” is a key element in the successful management of fragile or unstable patients.

4. Uncertainty regarding the needed dose of medication (e.g., diuretics) often can be addressed, valuable time can be saved, and prescription errors can be avoided by verbalizing therapeutic intent and boundaries to the nurse and writing goal-oriented orders when possible to do so.

5. Concerned family members may seek or be offered information from multiple caregivers with differing perspectives, knowledge, and attitudes. One or two physicians must be identified as the primary contact(s) and one responsible family member identified as the conduit for important medical interchanges. To maintain confidence, the family must understand the logic of current and planned management, possible outcomes, and contingency plans. Each ICU needs to establish and enforce a policy for family-caregiver communications that encourages trust, inspires confidence, meets the emotional needs of the family, and facilitates rather than impedes optimal care delivery.

6. Although certain consequences of protracted bed rest are well known to most practitioners, many subtle repercussions are either unknown or ignored. Physiologic adaptations to gravity affect nearly all organ systems, and release from gravitational stress may set in motion changes that delay recovery. Unrelieved recumbency has adverse implications for the respiratory, cardiovascular, and neuromuscular systems. The post-intensive care syndrome of lingering disability may be in large part the unintended and preventable result of ICU management.

7. Bedridden patients must be repositioned every 2 hours unless there is an important contraindication to do so. Head-up positioning (Fowler’s, reverse Trendelenburg, sitting positions) helps maintain vascular reflexes and reduces the tendency for peridiaphragmatic (basilar) atelectasis. The lateral decubitus and prone positions effectively stretch and drain the nondependent lung. Modern air-cushioned beds effectively distribute weight and shift the points of greatest pressure to preserve skin integrity.

8. Anxiety and pain occur almost universally in the ICU setting. The skillful team blends the use of anxiolytics with psychotropics, analgesics, physical measures, environmental modifications, and effective two-way communication. Attempts to encourage “normal” sleep-wake, lighting, and activity cycles may include “batching” of the routine monitoring observations and patient manipulations as well as the systematic use of hypnotics, analgesics, and anxiolytics where appropriate. Early intervention and the synergistic use of psychotropics (e.g., olanzapine, quetiapine) help alleviate pain and disorientation.

9. Aggressive respiratory therapy is essential to the care of patients with impaired lung expansion, retained
secretions, and bronchospasm. These techniques, which include repositioning, deep breathing, assisted coughing, aerosol inhalation, and chest physiotherapy, must be targeted to the specific problem at hand and used only as long as clearly indicated—either as prophylactic measures or as treatments of demonstrated benefit.

10. Inspired oxygen can be supplemented by nasal prongs, closed or open face mask, high-flow nasal cannula, or sealed airway (endotracheal tube). The selection is influenced by the range and precision of the FiO\textsubscript{2} required, patient tolerance, and the empirical response.

**BEDSIDE EVALUATION OF THE CRITICALLY ILL PATIENT**

**Therapeutic Perspective**

Certain important aspects of management are independent of the precipitating cause for ICU admission. These background details of day-to-day nursing and respiratory care help determine the eventual success or failure of specific management approaches leveled at the primary problems. This chapter reviews the basic elements of evaluation and therapy that apply to most patients in an intensive care unit (ICU) environment.

The term *intensive* care implies the potential for rapid changes in clinical status. Therefore, the patient must be monitored carefully, and the lines of communication among caregivers must be kept open. To care for the most critically ill, a knowledgeable and responsive physician must be continuously accessible and committed to reevaluating the patient as often and as long as required. The complexity of many critical illnesses demands that the physician evaluate each case from a strong background in physiology, intervene thoughtfully but promptly when indicated, and reassess frequently. There must be a short “feedback loop” linking intervention, result, and midcourse correction. In a field in which many key disorders are poorly defined (acute respiratory distress syndrome [ARDS], sepsis, etc.), it is often impossible to apply with confidence the results of population-based clinical trials to the individual patient. Decision support tools such as computer-aided access to the entire electronically encoded medical record and medical literature make impressive contributions to the goal of correct and timely intensive care. Remote access, however, cannot take the place of frequent bedside visits and effective verbal communications regarding goals, problems, and progress.

Communications concerning a complex database are often too severely strained by long-distance discussions for optimal care. In recent years, however, advances in telecommunications have facilitated economical and timely transfer of massive data files (e.g., as required for imaging and streamed video), thereby improving decision-making at a distance. Although not yet equivalent to bedside evaluation, such techniques are rapidly improving. They clearly offer the future possibility for care delivery at a uniform standard “24/7” or for a single specialty-trained physician to be involved simultaneously in the advanced care of multiple patients at different sites.

Although isolated measurements are unquestionably important, *trends* in the data stream are often of equal or greater value. For many variables, the trending interval ideally should include the prehospital period. Answers to such questions as “What is the patient’s chronic blood pressure, body weight, cardiac rhythm, blood chemistries, outpatient medication list, or PaCO\textsubscript{2}?” may determine the appropriate management goals during critical illness.

The ICU practitioner must intercede quickly and decisively when action is clearly necessary. In most circumstances, however, the clinician’s primary objective should *not* be to reestablish “normal physiology” as quickly as possible but rather to encourage compensation for or adaptation to the pathophysiologic insult. A working diagnosis and updated plan of action must be clearly formulated and communicated. Because the clinician cannot always foresee the consequences of intervention, it is important to question the data quality and to consider alternative explanations before acting. What really is known for certain and what must be better
Elements of the Bedside Evaluation

It is important to efficiently probe, organize, prioritize, and integrate the extensive body of information flowing from verbal and written communications, monitored data, laboratory output, and imaging studies (Table 18-1). Using the available database and his/her own observations at the time of evaluation, the physician formulates a listing of current problems, ranks their urgency and relative priority, and thoughtfully devises a plan of action. When things become hectic and/or risks are high for errors of omission or commission, 5 or 10 minutes spent away from the bedside in a quiet setting to analyze the database, identify the major problems and possibilities, and decide on the best management approach nearly always is time well invested.

Table 18-1. Elements of the Bedside Evaluation

<table>
<thead>
<tr>
<th>VERBAL COMMUNICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregivers</td>
</tr>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>Family</td>
</tr>
<tr>
<td>Referring physician or institution</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TEXT COMMUNICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electronic chart record</td>
</tr>
<tr>
<td>Nursing notes</td>
</tr>
<tr>
<td>Current orders</td>
</tr>
<tr>
<td>Medication/therapy lists</td>
</tr>
<tr>
<td>Data board</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LABORATORY RECORD</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>IMAGING STUDIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiology</td>
</tr>
<tr>
<td>Bedside ultrasound</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PHYSICAL EXAMINATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital signs</td>
</tr>
<tr>
<td>Systems review</td>
</tr>
<tr>
<td>Directed examination</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MONITORED INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator</td>
</tr>
<tr>
<td>Hemodynamics</td>
</tr>
<tr>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>Other apparatus</td>
</tr>
</tbody>
</table>

Caution is indicated whenever making management decisions without diagnostic certainty. Conducting a directly observed “minitrial” is often a key element in the successful management of a fragile or unstable patient,
especially when the physician is uncertain regarding the likely outcome of a planned intervention. After the evaluation has been completed and a course of action has been decided, the patient and physician are then better served by implementing the proposed order. This approach is particularly helpful when making ventilator adjustments, position changes, or alterations in the infusion rates of fluids or rapidly acting drugs, the effects of which can be monitored directly (see “Volume Challenge” in Chapter 2).

Accessing the Decisional Database

Skillful ICU practitioners not only pull together a vast array of data pertaining to the individual under treatment but also bring to bear the most appropriate therapy. Many decisions need to be made very quickly, and securing the needed information has the potential to consume enormous time. Faced with uncertainty and many competing priorities, the temptation is strong to forgo making a decision, to rely on memory, or to trust the verbal counsel of readily available colleagues. Potential for error and, consequently, the opportunity to improve care are high. The dramatic recent development of computer and communications technology has enabled partial closure of the information gap. Transitioning from paper records over a few short years, most physicians now make active use of computerized medical records and have remote digital access to laboratory data and imaging studies from unit-based workstations or personal computers. Impressive displays of trended information as well as raw and processed data can be configured to the user's specific needs. Powerful search engines (e.g., www.pubmed.gov) rapidly identify and retrieve relevant articles from the medical literature. Timely information access is aided by applications that package vital references, drug information, and periodically updated digests of evidence-based practice (e.g., Up-to-Date). Wireless Internet connections allow access to the health care system's own local network for timely retrieval of patient-specific data. Without question, the benefits and caregiving consequences of this extraordinary leap into the information age have been far reaching.

Verbal Communications and Bedside Rounds

As most experienced practitioners realize, the ICU tends to function best with a team approach in which caregivers of varied descriptions (physicians, nurses, therapists, pharmacists, etc.) are professionally acquainted, mutually respected, and equally committed. All must be apprised of the current therapeutic objectives. The day-to-day routines and the expectations for the unit must be well understood, ideally with an awareness of the work schedules and priorities of all involved. Despite the unquestioned value of “hard data,” over reliance on “the numbers” to guide decision-making fosters an immature, disconnected, and dangerous style of practice.

Drawing from moment-by-moment observations made at the bedside over extended periods, a well-trained nurse or therapist is often the caregiver with the best insight regarding the relation of events and medications to evolving problems, tolerance of current therapy, and the probable effects of intended interventions (weaning from mechanical ventilation, mobilization, transport, reaction to medication, mental status, airway secretions, etc.). The clinician must seek their active involvement and advice in the planning process. For the team to operate with maximum effectiveness, the nurse, respiratory therapist, and unit pharmacist (if available) should make formal rounds at least once daily with the intensivist physician to share observations and advice as well as to be kept abreast of the doctor's current thinking and care plan. Because everyone's time is valuable, the structure of these work conferences should be designed to recognize their commitment and to encourage helpful interchange (Fig. 18-1). The specific objectives of therapy and conditions or developments for which the doctor desires to be contacted should be communicated explicitly. Enormous benefit accrues from well-thought-out protocols as well as goal-directed orders that allow for modification depending on patient response. Uncertainty regarding the appropriateness and dosage of certain medications often can be addressed, valuable time can be saved, and prescription errors can be avoided by communicating the intent of treatment.
The latter strategy lends flexibility and allows timely adjustment (e.g., for fluids and/or diuretics). A very common error is to write an order, to assume that it was carried out, and then to fail to follow up on the result of its execution. Setting clear goals for the nurse or the therapist, allowing for “real-time” modification of dosing in accordance with those goals, and automatic notification when the goals cannot be met tighten the linkage between patient and caregivers. (“Adjust the furosemide drip to maintain output > input by at least 1 L per shift” is more likely to succeed than “Give 40 mg furosemide IV TID.”) Goal-directed order writing extends many of the same advantages offered by formalized care protocols (e.g., for heparin adjustment or insulin delivery) to a much broader and less constrained therapeutic context.

- **Intensivist-led bedside rounds that encourage team interactions**
  RN, RT, Pharmacist, Nutritionist, Residents/Fellows, Advanced Practice Providers
- **Start and end rounds on time**
- **Define and communicate rounding roles and expectations for everyone**
- **Structure the process to cover the major domains of the database**
- **Stay focused on management and do not spend longer than needed**
- **Teach “on the fly” when directly relevant to the patient’s management**
- **Minimize interruptions**
- **Encourage family participation when appropriate**
- **Measure quality of rounds**
  Seek critical/constructive feedback

**FIGURE 18-1. Suggestions to conduct effective multidisciplinary bedside rounds.** (Modified from Dr. Steven Pastore, personal communication.)

**Family Communications**

It is difficult to overestimate the importance of frequent, direct, unambiguous communication with the family. The ICU environment holds undeniable potential for miscommunication as the concerned family member may seek or receive information and advice from many caregivers with differing perspectives, knowledge, and attitudes.
Generally speaking, trust in the fast-paced, high-tech unit and in the care team that makes potentially lifesaving or life-threatening decisions has eroded somewhat over the years. Respect and engagement are the two watchwords. Families usually wish to know the “real story” and to understand the perceptions and approach—primary and contingency plans—of the attending physician. The family should be encouraged to join the rounding team during the visit to their relative's bedside. They often provide useful information and observations otherwise difficult to come by. If care is obviously futile or should be withdrawn, a frank private discussion is advisable, especially if the family has initiated the conversation. But if the outcome is uncertain and there are logical steps to be taken to reverse the crisis, the family needs to know this as well. They also must perceive the physician's positive attitude toward resolution of the illness, whenever this is valid, realistic, and possible to convey. Telling the family that there is little hope when the situation is ambiguous may alienate the family when they perceive that the team is not genuinely trying or has already given up.

The characteristics that patients recognize in an excellent doctor include not only professional expertise but also humanistic qualities such as truthfulness, patience, respecting patient preferences, attentiveness, advocacy of patient interests, and thoroughness. Time spent with the patient ranks high among the valued traits. The most frequent characteristics of excellence in ICU physicians cited by their peers are knowledge, outstanding clinical skills, commitment, enthusiasm, and compassion. Perhaps not surprisingly, nurses value interpersonal skills, approachability, attentiveness to family, commitment, and ease of communication among the most appreciated physician traits.

The tone and content of communication should not always be serious—light humor does wonders to bridge the gap between caregiver and the vulnerable recipients of care. One or two physicians must be identified as the primary contact(s). Clearly, the family must be allowed to visit the patient as soon as appropriate after admission or in an unanticipated emergency. Continual presence of at least one family member at the bedside may be culturally mandated. In fact, there is a strong trend to design or modify ICUs so that the family can remain close to the patient at all times and be encouraged to directly observe and understand many aspects of care that were previously “out of bounds.” Recently published data support this newer shift in practice. Even though some ICUs maintain unrestricted access to the patient with the best of intentions, many others believe it wisest to restrict routine visiting hours to two or three predictably “quiet periods” in the workday (e.g., late morning, late afternoon, early evening), especially in high-acuity ICUs. The approach should be individualized. Continual contact often threatens to confuse and emotionally exhaust the worried family, seldom benefits the comatose or sedated patient, encourages interchange of microbial pathogens, and may interfere with caregiving. Whatever the local policy, it is wise to set aside a time in the day when physicians reliably communicate progress and plans and receive vital feedback from family members. Some well-functioning units reserve a specific hour each day (e.g., 1:00 to 2:00 pm) during which a physician team member can be scheduled (by the unit clerk) to discuss progress and plans with the patient's relatives. To reduce the emotional strain on both family and staff in an inherently unstable environment, it is important to emphasize that monotonic improvement (although the desired goal) is not the rule, that minor setbacks and complications are to be anticipated, and that it is often most appropriate to view the general trend over days to weeks—not minutes to hours. Clearly defining the likely diagnoses and plausible alternatives, the team's approach, the strategy for action, and contingency plans help build confidence and trust.

The experience of receiving intensive care is simultaneously isolating, frightening, and disorienting; perhaps never before has the patient felt as powerless, vulnerable, or dependent on others. Apart from expressing compassion, efforts to alleviate such distress and improve mental well-being might conceivably speed the rate of recovery. Clearly, some forms of organ system dysfunction or disease (such as sepsis and ARDS) impair brain functioning, perhaps contributing to delirium. Conversely, certain forms of brain dysfunction hold potential to disrupt homeostatic responses and adversely influence vital organ health. Scientific investigation of such two-
way brain-organ cross talk during critical illness is an emerging field of neuroscience that has begun to attract investigative attention (Fig. 18-2). The imposed monotony of critical care disrupts the normal variability of homeostatic stresses and adjustments, adding to the adverse conditioning of brain, muscles and psyche.

Almost invariably, the ICU experience is life-disrupting and anxiety provoking for family and close relations as well. Establishing trust with the caregivers is vital to alleviating worry and achieving compliance with indicated measures. Seriousness, honesty, and respect must be conveyed whenever addressing medical issues. A clear plan and contingency arrangements must be communicated to reinforce the perception that the clinician is truly the patient's advocate and that the situation—however difficult—will be appropriately addressed.

Intubated patients cannot verbally express needs, sensations, or emotions. Familiar photographs, a clock plainly visible to the patient, and a readable calendar help maintain proper orientation. Although no strategy works effectively for all patients, caregivers should remain sensitive to the possibility of hearing or sight impairment.
The fact that the patient normally wears a hearing aid or uses glasses may be forgotten in the highly charged, technology-driven setting of the ICU. Alert patients may be able to express basic needs or pose questions via note writing, lipreading, letter boards, or graphic charts. Close friends and family members may interpret gestures more effectively than the medical staff, especially if the patient has been chronically disabled. For patients with tracheostomies who require ventilator support, cuff deflation allows vocalization if positive end-expiratory pressure (PEEP) of about 10 cm H₂O is applied to provide adequate leakage airflow across the vocal cords. Patients with adequate strength who are not ventilator dependent and breathe spontaneously can speak through a one-way (Passy-Muir) valve attached to the cuff-deflated tracheostomy tube. For patients who are fully alert and sufficiently strong, written messages offer an effective, albeit tedious, method of interaction.

**Communications and Records**

In addition to discussions with other caregivers, the physician must review the chart record, nursing notes, orders, medication and therapy lists, recorded bedside data board, ventilator sheet, and laboratory record. Increasingly, all such information is incorporated into an electronic medical record (EMR), and caregivers are given direct responsibility for detailed documentation. This new emphasis on electronic documentation—in many cases designed as much as a billing instrument than a communication tool—has given rise to templated notes laden with “cut and paste” entries and unnecessary replication of laboratory data. The need to communicate and document through the computer has taken its toll on effective communication among caregivers, and the time crunch discourages the physician from returning to the bedside after morning rounds. Just how the benefits and detriments of the EMR play out in the ICU has yet to be fully understood.

The need to carefully review the current listing of medications with the patient's ongoing and resolved problems clearly in mind cannot be overemphasized. To prevent delays and errors, it is a good idea to enter intended orders at the time of the bedside visit, and the presence of an ICU specialized pharmacist is an invaluable help. The nursing record often provides an overlooked and valuable source of information. Puzzling entries with the potential to influence decision-making should be clarified by direct verbal communication. Calculations required to synthesize the clinical picture and formulate revisions to the care plan (e.g., anion gap, systemic vascular resistance, respiratory compliance, airway resistance) should be automated or made quickly available at the bedside. Specific attention should be directed to the patient's weight, net fluid balance, intake, urinary and fecal output (Ins and Outs), diet, and drugs (those scheduled and those given as needed). Sedatives, antibiotics, vasoactive agents, and diuretics tend to be of special interest. The volume and description of expectorated or suctioned airway secretions and gastric aspirates should be noted.

**Laboratory Data**

The most recently obtained values for arterial blood gases, hemoglobin concentration, leukocyte and platelet counts, serum glucose, blood urea nitrogen (BUN), creatinine, electrolytes, and urinalysis must be reviewed in every patient for whom they are available. Serial tests for liver or cardiac enzymes, leukocyte differential, coagulation profile, drug levels, and renal function tests may be of unusual interest in specific patients. As already noted, trends in such data often are more meaningful than are individual test results.

**Physical Examination and Monitoring**

The contribution of the physical examination has become devalued as our technical abilities to image noninvasively, to monitor cardiorespiratory function, and to use laboratory data have improved. However, certain key bits of information that are impossible to gather quickly by other means should be assessed by physical examination one or more times daily in virtually every patient with cardiorespiratory instability or compromise. Although the directed physical examination is the practical standard, outstanding clinicians are
sufficiently disciplined to quickly but systematically assess certain aspects of the physical examination each day, not only to detect areas of concern but also to develop the background against which to gauge any future changes.

**Vital Signs**

Review of the vital signs record is a frequent starting point in the bedside evaluation. What are often overlooked, however, are the degree of variability and telling relationships among individual parameters. For example, heart rate may not parallel the height of fever or may be inappropriately slow for the clinical setting of congestive failure, as suggested by a disjunction between elevations of heart rate and respiratory rate. Extreme respiratory variation evident on an arterial or pulse oximetry tracing suggests relative hypovolemia and/or the paradox associated with severe airflow obstruction, severe left heart failure, or pericardial disease. Vital signs may change markedly with sleep or level of alertness. In the ventilated patient who makes spontaneous efforts, minute ventilation should be considered a vital sign. Wide variations of minute ventilation, especially when they occur abruptly, suggest that agitation may be responsible for the higher values. (This variability becomes an important consideration when prescribing sedatives and analgesics and when evaluating the ventilation requirements of a weaning candidate.)

**Mental Status and Neuromuscular System**

The categories of the Glasgow Coma Scale serve as a reminder of the gross characteristics to be screened and followed: best verbal, motor, and eye opening (and pupillary) responses. Muscle tone and strength, facial appearance, eye movements, pupillary size and reactivity, peripheral reflexes, and asymmetry should be noted. Signs of fear, anxiety, depression, and delirium should be elicited actively by attempting to engage the patient in meaningful conversation as well as light banter. (A well-timed sense of humor tests high-level integrative mental capacity, builds trust, reduces anxiety, and serves to narrow the communication gulf that separates patient and physician.) It is important to question the nursing staff regarding how well the patient has been sleeping, especially if delirium is suspected, dyspnea is questioned, or weaning is contemplated.

**Cardiovascular System**

Sequential cardiovascular examinations can reveal a new gallop, murmur, rhythm disturbance, paradoxical pulse, neck vein distention, basilar rales, dryness of the mucous membranes, diaphoresis, edema, impaired capillary refill, and other signs that provide clues to underlying pathophysiology. This knowledge should be interpreted in conjunction with an examination of electrocardiographic and arterial pressure tracings, echocardiogram, bedside ultrasonic and radiographic information, and mixed venous, filling pressure and cardiac output data, when available. Serial examinations are especially important in the setting of myocardial infarction, acute endocarditis, or other potentially life-threatening, rapidly changeable conditions.

**Respiratory System**

Consecutive physical examinations of the respiratory system should focus on the quality, intensity, and symmetry of breath sounds; the presence or absence of regional percussion dullness; the breathing pattern; the audibility and distribution of wheezes, rales, rhonchi, and bronchial breath sounds; and the vigor and effectiveness of breathing efforts. Pulse oximetry can be extremely helpful when adjusting inspired oxygen fraction (FiO₂), PEEP, position, or ventilator settings. Mechanically ventilated patients require a careful review of the record documenting minute ventilation, oxygen, pressure requirements (peak, mean plateau, PEEP, and driving), gas exchange efficiency, patient-ventilator synchrony, integrity of the breathing circuit, and machine mode and settings (as detailed in Chapter 5).

**Renal and Electrolyte Status**

Although urine output and composition often should be followed closely, not every patient in the ICU requires an indwelling bladder catheter. However, because the urinary output of the healthy kidney tends to
parallel intravascular fluid volume and serves as a useful indicator of vital organ perfusion, patients with questionable cardiovascular status often need continuous urinary output recording. The clinician should allow a trend to evolve over 1 to 3 hours before making radical interventions based primarily on urinary output because oliguria may be transient or may respond only slowly to corrective action. Moreover, it is prudent to keep in mind the recent changes in therapy, cardiovascular status, sleep-wake cycles, and serum electrolytes in making the interpretation. The color, pH, specific gravity, glucose and electrolyte concentrations, results of tests for leukocyte esterase, erythrocytes, hemoglobin, and a review of sediment characteristics and pending urine cultures aid in assessing fluid status as well as in determining the etiology and severity of many common disorders. BUN and creatinine should be compared with previous values. These data should be considered in conjunction with the daily and cumulative I&O record, the daily weight trend, and the listing of medications in assessing the fluid balance. Weight should be compared with those of previous hospital days and the admission value, as well as with weights recorded previously in outpatient clinics or prior admissions. Arterial blood gases and serum electrolytes should be reviewed, and anion gap and serum osmolality should be estimated.

**Gastrointestinal/Nutritional Status**

Daily assessments should include a review of nutritional intake. The volume and character of gastric aspirates and stool output also must be tracked. To evaluate gut motility, the physical examination of the abdomen always should include auscultation. The persistent absence of stool or gas output despite enteral intake may suggest obstipation or bowel obstruction, especially when the abdomen becomes noticeably distended. When confronting a quiet abdomen, it is important to palpate deeply and to attempt to elicit signs of peritoneal inflammation. Ascites, excessive bowel gas, gastric distention, and gut edema may explain a visibly distending abdomen. A “tight belly” may explain high ventilator cycling pressures or, if extreme, a dwindling urinary output. In such cases, bladder pressure should be transduced and measured (see Chapter 5).

**Apparatus**

Extensive use of equipment and devices characterizes the care delivered to critically ill patients. Intravascular lines and pumps should be inspected quickly, and their sites of entry should be examined for evidence of phlebitis, local cellulitis, or purulence. The dressings that cover suspicious points of catheter insertion must be taken down and the wound beneath must be examined carefully, preferably at the time of routine dressing changes. When specialized life-support equipment is used (e.g., balloon pump), the key variables relevant to its operation and the level of support must be noted. Enteral catheters and endotracheal tube anchoring devices should be inspected and the ventilator circuit examined for collected water. The essential data provided by the bedside cardiac monitor and the ventilator display are reviewed with each visit to the bedside.

**Imaging Data**

Radiographs, computed tomograms (CT), and ultrasonic images have become integral to the evaluation of the critically ill patient (see Chapter 11). Rounds should incorporate a review of such data, which often redirect thinking or confirm diagnoses made by other means.

**THERAPEUTIC SUPPORTIVE CARE**

Intensive life support has no evolutionary precedent. Before modern civilization, our primate ancestors were at constant risk of predatory attack and disease. Survival required foraging and continuous vigilance; our
predecessors seldom remained off their feet or motionless for longer than a few hours at a time. Most conditions that now prompt admission to the ICU would previously have resulted in a quick demise. Deprived of food and water and unable to take shelter from the elements and natural enemies, the sick individual became vulnerable to many of the traumatic, infectious, and environmental problems that now are easily manageable. A philosopher or anthropologist could argue effectively that evolutionary pressures encourage elimination (rather than survival) of those weak enough to fall prey to catastrophic disease or severe trauma.

**Post-ICU Syndrome (PICS)**

It has become clear that for too many, the seemingly optimistic short-term triumph over a life-threatening critical illness symbolized by ICU discharge represents a pyrrhic victory, in that lingering physical and psychological difficulties too often degrade the quality of daily life afterward. Long-term outcomes in survivors of critical illness include not only the well-known disorders of the nerve, muscle, and central nervous system but also a constellation of varied physical consequences that range from joint contractures to tooth loss and distressing alterations of facial appearance and body image. Compromised quality of life relates as much or more to impaired physical, social, emotional, and neurocognitive functions as to discrete cardiopulmonary disabilities (e.g., ARDS) that prompted the ICU admission. The prevalent ICU-acquired weakness syndromes manifest in various ways, and some are selective enough in their manifestations to merit labels, such as critical illness polyneuropathy and myopathy. Patients with sepsis and those receiving high-dose steroids for lengthy periods may be at heightened risk for losing muscle strength upon recovery. However, the more commonly encountered forms of weakness are almost ubiquitous after an extended ICU stay and undoubtedly have widely shared pathologic, therapeutic, and nutritional components. Disturbingly, recovery from these lesions may remain incomplete for years after ICU discharge. Mental impairments also tend to follow the patient who returns home. Cognitive impairment in ARDS survivors, for example, has been reported to exceed 70% at hospital discharge and persists to some degree in more than half of these for the following year. Mood disorders, including depression and posttraumatic stress disorder (PTSD), are also prevalent. For what might seem to be obvious reasons, family members of critical illness survivors are also adversely affected. Useful interventions to improve these outcomes, for example, prevention and early treatment of delirium and early mobilization, are certainly promising but still unconfirmed. Data in the current medical literature conflict, and we do not yet understand enough. However, it makes good intuitive sense to minimize unnecessary interventions while the patient is under intensive care and to try to restore more normal activity patterns as soon as feasible to do so. Keeping the patient at bed rest is clearly not one of them.

**Physiology of Prolonged Bed Rest**

**Noncardiorespiratory Effects of Sustaining the Recumbent Position**

Because lengthy periods in the recumbent position are central to extended life support but inherently unnatural, a working knowledge of the physiology of sustained bed rest and immobility is fundamental to understanding the rationale and sequelae of ICU confinement. Certain consequences of protracted bed rest are well known to most practitioners, whereas other, subtler repercussions are either unknown or ignored. Physiologic adaptations to gravity affect nearly all organ systems, and release from gravitational stress may set in motion changes that impede recovery.

**Neuromuscular**

While under the influence of gravity, contracting skeletal muscles compress the veins and lymphatics, counteracting the gravitational forces that would otherwise cause the body fluids to pool in the legs and lower
abdomen. Contraction of muscles used in maintaining the upright posture and locomotion preserves muscle bulk and strength. Symmetry of upper as well as lower extremities should be noted and tracked. Lack of movement, hypoalbuminemia, and the persistently upright torso encourage edema to form in the hands and the lower arms. Asymmetry of the edema that forms suggests an upper extremity thrombosis—which occurs quite commonly in patients with ipsilateral PICC and subclavian or internal jugular catheters. Moreover, muscular traction and gravitational stresses help the bones retain calcium. It is not known what level of fiber tension or duration of contraction is necessary to sustain these benefits. It is clear, however, that release of the skeletal muscles from their diurnal activity for longer than 24 to 48 hours initiates metabolic processes that eventually culminate in tissue atrophy and impressive physiologic changes.

Aerospace science and experiments in healthy volunteers have yielded impressive data on the effects of bed rest in healthy individuals (Table 18-2). Skeletal muscles quickly lose tone when not supporting the body’s weight. After only 72 hours, the loss of myofibrillar protein is under way—even in a well-nourished, physiologically unstressed subject. The greatest protein losses occur in the muscle groups that normally bear the greatest postural burden—legs and dorsal trunk. The rates at which bulk and strength diminish are believed to be functions of the length at which the muscle fiber is immobilized as well as the completeness of relaxation. As indicated by the devastating weakness that results from extended pharmacologic paralysis, neural excitation may be a crucial factor in preserving muscle function. Intense stimulation may not be required to dramatically slow the pace of sarcomere depletion, and although active movement is clearly better than passive manipulation of resting muscle, physical therapy of the immobilized patient aids significantly in preventing contractures.

### Table 18-2. Physiologic Effects of Sustained Bed Rest

<table>
<thead>
<tr>
<th>NON-CARDIORESPIRATORY EFFECTS</th>
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<tbody>
<tr>
<td>Reduced muscle bulk and strength</td>
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<tr>
<td>Altered biorhythms</td>
</tr>
<tr>
<td>Decreased glucose tolerance</td>
</tr>
<tr>
<td>Endocrine dysfunction</td>
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<tr>
<td>Fluid shifts and diuresis</td>
</tr>
<tr>
<td>Calcium, potassium, and sodium depletion</td>
</tr>
<tr>
<td>Immunologic impairment</td>
</tr>
<tr>
<td>Nasal congestion/impaired sinus drainage</td>
</tr>
<tr>
<td>Reduced gastrointestinal motility/esophageal reflux</td>
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<table>
<thead>
<tr>
<th>CARDIOVASCULAR EFFECTS</th>
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<tbody>
<tr>
<td>Pulmonary vascular congestion</td>
</tr>
<tr>
<td>Impaired vasomotor tone and reflexes</td>
</tr>
<tr>
<td>Increased preload and stroke volume</td>
</tr>
<tr>
<td>Altered autonomic activity</td>
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<table>
<thead>
<tr>
<th>RESPIRATORY EFFECTS</th>
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</thead>
<tbody>
<tr>
<td>Reduced functional residual capacity</td>
</tr>
<tr>
<td>Altered distribution of lung volume</td>
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<tr>
<td>Altered airway drainage</td>
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</table>
As any sleepless physician understands, periodic rest in the recumbent position is essential for optimal cerebral functioning. Even during sleep, however, the healthy adult turns or makes a significant positional adjustment multiple times per night. As noted in the following, there may be important physiologic advantages to such frequent repositioning. Most adults do not prefer to initiate sleep in the supine horizontal position that is used routinely in the ICU. Many individuals express great difficulty in falling asleep in this position or awaken quickly if they inadvertently shift into it. In fact, all nonarboreal four-footed mammals—including the primates—ambulate prone, with vulnerable vital structures protected by proximity to the ground. Most animals sleep in that position as well.

With the development of modern intensive care and the need to cannulate blood vessels and access the various orifices of the respiratory, gastrointestinal, and urinary systems, the recumbent critically ill patient was kept oriented in the supine position for extended periods, often immobilized by sedation or paralyzed pharmacologically by muscle relaxants. Periodic turning is known to be important in the avoidance of pressure trauma (decubitus ulcers, see following), which is most likely to develop over the points of high contact pressure—especially when the patient is cared for on a firm traditional bed. (Perhaps such vulnerability helps explain the need for frequent movement during sleep.)

**Endocrine and Metabolic (see Chapter 32)**

Release of many hormones normally is timed to a diurnal cycle. For example, cortisol and epinephrine normally vary in a circadian fashion, with trough levels occurring in the early morning hours. Cholinergic (vagal) tone and melatonin release (a hormone that regulates immune and certain endocrine functions as well as wakefulness) also increase at night. The unnatural activity patterns, body manipulations, sedation patterns, lighting, and noise within many ICU environments disrupt these natural diurnal/circadian cycles. Moreover, bed rest itself alters certain biorhythms; cycles for insulin and growth hormone (and consequently glucose) often demonstrate multimodal patterns, time-shifted peaks, and other perturbations in normal healthy subjects, even when feeding schedules remain unchanged (Fig. 18-3). The activity of the pancreas gradually declines, and glucose intolerance may develop after as little as 3 days of enforced bed rest. These changes usually reverse within 1 week of resuming normal activity. Thyroid hormones tend to rise as bed rest continues beyond a few weeks, whereas androgen levels fall. Oxygen consumption declines significantly during recumbency.

**Fluid and Electrolyte Shifts**

Recumbency shifts about 10% of the total blood volume (approx. 500 mL) cephalad, away from the legs. Almost 80% of the shifted volume migrates to the thorax; the remainder translocates to the head and neck. The nasal mucosa swells, and the patient may experience nasal congestion. Diuresis begins on the first day of recumbency for the normal subject, who loses approximately 600 mL of extracellular fluid by the second day (more if edema was present initially). Bed rest initiates losses of sodium and potassium but reduces the amplitudes of the diurnal excretory cycles for water, sodium, potassium, and chloride. Weight bearing seems to be an important stimulus to osteoblastic activity, and during prolonged bed rest, approximately 0.5% of total body calcium stores are leached per month from the bones and muscles. Rarely, impaired renal excretion of the increased calcium load results in hypercalcemia.
Gastrointestinal Changes
Well-known gastrointestinal responses to inactivity include anorexia and constipation. Recumbency impairs the efficiency of swallowing and may precipitate esophageal reflux in those with lax esophageal sphincter tone. The gut may lose all but a vestige of its natural motility if food is not provided, gastric secretion is pharmacologically suppressed, and air swallowing is inhibited—even if opiates are not prescribed (see Chapter 17).

Immunologic Defenses
Bed rest impairs the body’s resistance to infection, even when no catheters enter the vascular, urinary, respiratory, or gastrointestinal compartments. The normal rate of catabolizing immunoglobulin G doubles, and neutrophilic phagocytosis slows. The mucosal colonization rate for certain pathogens, such as the staphylococcus, may increase. An adverse gravitational bias results in stasis, secretion pooling, and bacterial overgrowth within the maxillofacial sinuses and tracheobronchial tree—further predisposing patients to infection.

Blood Components and Coagulation
It generally is understood that patients on protracted bed rest are vulnerable to thrombosis—largely because of venostasis and unrelieved compression of the leg veins. Subtle changes also occur in the coagulation profile; procoagulant synthesis and fibrinolytic activity increase, and the thromboplastin time shortens. Independent of any coexisting disease process, the red blood cell mass tends to decline during the first several weeks of inactivity, primarily because of a decrease in erythropoiesis.

Cardiovascular Effects of Recumbency
Vasomotor changes in arterial resistance both maintain blood pressure relatively constant and regulate the distribution of blood flow. In the active and fully conscious normal individual, fluctuations in regional tissue blood flows occur naturally and spontaneously. In the immobile supine patient, these fluctuations gradually disappear over the first hours of recumbency. Subjects forced to remain alert and at bed rest may then experience sufficient discomfort to impel a change in position.

Many significant cardiovascular changes occur in the healthy individual during the transition to the supine position (see Table 18-2). In the conscious normal subject, heart rate declines slightly and stroke volume increases. Cerebral, renal, and hepatic blood flows increase, whereas blood pressure and systemic and pulmonary vascular resistances tend to decline. Sympathetic tone decreases, and parasympathetic tone
increases. The renin-angiotensin axis down-regulates, promoting diuresis. The baroreceptive reflexes that are instrumental in adapting to the upright position are blunted after sustained bed rest; therefore, chronic orthostatic stress seems necessary, both for the preservation of an adequate blood volume and for maintaining adaptive cardiovascular reflexes.

The Trendelenburg (head-down) position offers no significant hemodynamic benefit over that provided by the supine position, and despite its widespread use, it has no confirmed place in the management of shock (other than for central line placement). The gravitational bias of the Trendelenburg position increases intracranial arterial and venous pressures equally and, therefore, leaves cerebral perfusion unimpaired in normal individuals. However, further elevation of intracranial pressures may compromise cerebral perfusion in the patient with preexisting head injury at baseline. Head inversion also increases the tendency for esophageal reflux. These drawbacks do not mean that the Trendelenburg position cannot be useful when used briefly for specific purposes; airways drain more effectively, and distention of neck veins facilitates the insertion of central venous catheters while helping to avoid air embolism.

Extreme flexion of the trunk in infants, obese adults, and advanced pregnancy may not only result in hypoxemia but also may impede venous return. For a woman in the advanced stages of pregnancy, lying in the supine position may compress the vena cava, causing hypotension that is relieved by lying on the left side. Increased abdominal pressure leading to inferior vena cava obstruction also has been associated with the prone position, especially when there is exaggerated knee-chest positioning or an unusually noncompliant abdominal support.

Respiratory System

Conversion from the upright to the supine position is accompanied by important changes in ventilation, perfusion, secretion clearance, muscle function, gas trapping, and tendency for and distribution of lung collapse. In normal subjects, recumbency decreases functional residual capacity (FRC), primarily because of the upward pressure of the abdominal contents on the diaphragm and to a lesser extent to declining lung compliance. The functional residual volume declines by approximately 30% (800 to 1,000 mL) in shifting from the sitting to the horizontal supine position and marginally less in the sitting to lateral decubitus transition. Patients with airflow obstruction generally lose much less volume in supine recumbency (Fig. 18-4). Head-down tilting causes only a marginal additional volume loss. The magnitude of these reductions is somewhat less in older than in younger patients. Massively obese patients often encounter special challenges when placed supine. When horizontal, the upward thrust of the abdominal contents increases pleural pressure in many, prompting early airway closure during exhalation. The usual 30 to 45 degrees angulation of the head of the bed may not be sufficient to prevent gas trapping and atelectasis. Higher than customary upper body positioning (60 to 75 degrees) or increased end-expiratory pressure is advised in these vulnerable patients, even in those without pre-existing lung compromise (Fig. 18-5).
FIGURE 18-4. Spirograms during a vital capacity breath in upright and supine positions for three types of patient. Although they start from decidedly different sitting baseline volumes, patients with severe COPD and obesity tend to lose less resting lung volume than do normal subjects when they recline, in part because of positional gas trapping.

Body rotational changes within the horizontal plane (e.g., supine to lateral or prone) do not dramatically change overall aerated volume, but the regional gas distribution is impressively altered. Thus, conversion from the supine to the prone position is usually accompanied by limited overall change in resting lung volume, but the distribution of regional forces changes markedly, especially in ARDS (see Chapter 24).

Position also influences pulmonary hemodynamics. Blood flows tend to distribute preferentially to the dorsal regions in both the supine and prone positions. Recumbency redistributes lung volume because it alters the geometry of the thorax. The heart tends to compress the left lower lobe bronchi and is supported partially by the lung tissue beneath. This anatomy helps account for the tendency for atelectasis to develop so commonly in the left lower lobe in postoperative and bedridden patients—especially those with cardiovascular disease. The pleural pressure adjacent to the diaphragm is considerably less negative than at the apex. The vertical gradient of transpulmonary pressure (alveolar minus pleural pressure) is approximately 0.25 cm H₂O per cm of vertical height for normal subjects in the erect position and approximately 0.17 cm H₂O per cm for normal subjects in recumbency; therefore, alveolar volumes are greatest in the nondependent regions. For patients with edematous lungs, an intensified gravitational gradient of pleural pressure accentuates dorsal atelectasis and consolidation.
FIGURE 18-5. Appropriate positioning for massively obese ventilated patient will help prevent airway closure and reduce the plateau and driving pressures needed to deliver a breath of a given size. Such patients often require quite high PEEP in more recumbent positions to keep airways open throughout the tidal breath.

The gradient of pleural pressure is considerably less in the prone than in the supine position, perhaps in part because of the shifting mediastinal contents and better shape matching between the lungs and their thoracic enclosure. The prone position also favors airway drainage. The lateral decubitus position causes the upper lung to assume a resting volume nearly as large as it has in the upright sitting position and to undergo better drainage, whereas the lower lung tends to pool mucus and is compressed to a size similar to or less than what it has in the supine position.

**Distribution of Ventilation**

During spontaneous breathing, ventilation distributes preferentially to the dependent lung zones in the supine, prone, and lateral positions. The normal subject also takes “sigh” breaths two to four times deeper than the average tidal volume approximately 8 to 10 times/h. Postural changes occur frequently. Microatelectasis and arterial O$_2$ desaturation tend to develop if breathing remains shallow and uninterrupted by these periodic sighs or variations of position. In contrast to spontaneous breathing, the nondependent regions receive the most ventilation when the patient is inflated passively by a mechanical ventilator. Dependent regions not only have the least end-expiratory (resting) lung volume but also receive less ventilation, further promoting atelectasis in those areas.

**Positional Dyspnea**

Certain positions may relieve or exacerbate dyspnea. Orthopnea, although most emblematic of congestive heart
failure, also characterizes severe airflow obstruction, pregnancy, extreme obesity, pericardial tamponade, and diaphragmatic weakness. Conversely, patients with quadriplegia or extreme orthostatic hypotension and those who experience abdominal or back pain accentuated by the upright position may not tolerate sitting without breathlessness.

**IMMOBILITY: PREVENTATIVE AND THERAPEUTIC MEASURES**

Against the physiologic background just described, it is clear that prolonged immobility must be avoided. For alert patients, mobilization to chair or ambulation should be strongly considered. For patients who have entered the recovery phase, active muscular exercise can be encouraged under direct observation (Fig. 18-6), even stationary cycling while in bed. For profoundly weak or pharmacologically immobilized patients, range-of-motion exercises and high-top tennis shoes or foot boards may help prevent foot drop. As a rule, bedridden patients must be repositioned every 2 hours unless there is an important contraindication (e.g., hemodynamic instability or spinal injury). Inclining the upper torso above the horizontal plane (Fowler's, reverse Trendelenburg, sitting position) helps preserve the vascular reflexes, limits the risks of esophageal reflux and aspiration, and reduces the tendency for peridiaphragmatic (basilar) atelectasis. The lateral decubitus and prone positions effectively stretch and drain the uppermost lung regions. Certain automated beds can effectively rotate the patient about the craniocaudal axis in an attempt to ensure such benefits and preserve skin integrity (see “Specialty Beds”).

**Skin Breakdown and Pressure Ulcers**

**Etiology**

When local surface pressures exceed capillary pressure, the resulting ischemia can produce necrosis of the integument. Developing breakdown of the skin over pressure points was once a common, costly, and preventable problem for critically ill patients. Pressure ulcers tend to prolong hospitalization and increase morbidity. When they occur, decubitus ulcers develop most frequently in elderly, emaciated, and/or diabetic
patients, but any patient with one or more of the major risk factors (high local pressure, increased shear force, friction, reduced capillary perfusion, anemia, malnutrition, tissue edema, or prolonged moisture exposure) is at risk. Because mechanically ventilated patients often are sedated or paralyzed, malnourished, edematous, hypotensive, or confined to bed for lengthy periods, they are especially vulnerable.

Pressure ulcers are most likely to develop over bony prominences where compressive forces may exceed the normal capillary filling pressure of approximately 25 to 30 mm Hg for an extended period, thereby promoting ischemic injury. Relieving local pressure is especially important for patients in the prone position, when the nose, chin, shoulders, knees, and hips are the contact points rather than the broad surface of the back and upper legs. Pressure ulcers also can develop without high compression when the skin is subjected repeatedly to friction or shear or becomes macerated because of prolonged exposure to urine or feces.

**Prevention and Routine Treatment Measures in the ICU**

Varied measures can be used to interrupt and reverse the progression toward ulceration (Table 18-3). The stages and seriousness of ulceration are scored from 1 to 4, and the propensity to develop pressure sores is widely evaluated by nurses on the Braden scale for prediction of pressure ulcer risk. Frequent repositioning and mobilization relieve local pressure and forestall skin breakdown. Massage of reddened skin and areas of bony prominence improves local circulation. Prevention of decubitus ulcers is one reason to avoid deep sedation or paralysis whenever possible. As already noted, adjustments of position occur frequently during sleep. Motionless patients should be repositioned no less frequently than every 2 hours, unless such manipulation disrupts wounds, impairs oxygenation, or promotes homodynamic instability. When frequent repositioning is not possible, careful padding of bony prominences and special padding of surfaces can help prevent injury. Many air-cushioned specialty beds limit and vary the gravitational forces applied to specific high-risk areas, decreasing the likelihood of skin breakdown (see following).

Preventing the development of pressure ulcers is much easier than treating the established lesions. Once established, however, more than 100 topical products can be brought to bear. These are organized into several categories: wet gauze, ulcer-covering films (e.g., Tegaderm), foams (e.g., Lyofoam), hydrocolloids (e.g., DuoDERM), hydrogels (e.g., Carrington), and alginates (e.g., Sorbsan). Each product group claims superiority in specific settings, and because of the complexity of this topic, it is best to consult a wound care specialist for significant problems. (Depending on the institution, this service may be offered by burn, wound, or plastic surgery professionals.) In the healing process, the importance of optimizing nutritional status, of avoiding extended moisture exposure (especially that due to incontinence), and of early mobilization cannot be overemphasized.

### Table 18-3. Prevention of Cutaneous Pressure Sores

<table>
<thead>
<tr>
<th>Prevention of high local tissue pressures</th>
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<tbody>
<tr>
<td>Avoidance of:</td>
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<tr>
<td>Malnutrition</td>
</tr>
<tr>
<td>Edema</td>
</tr>
<tr>
<td>Maceration</td>
</tr>
<tr>
<td>Ischemia</td>
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</tbody>
</table>
Mobilization

Topical coverings

Specialty mattresses and beds that alter body position through wide range

For patients whose decubitus ulcers fail to heal despite such measures, infection of the soft tissue or underlying bone is often responsible. To optimize healing, devitalized tissue should be debrided and appropriate antibiotics administered. Although the site of ulceration may influence the spectrum of flora recovered, infected wounds often contain a mixture of gram-positive cocci and gram-negative rods and anaerobes, making blanket antibiotic recommendations difficult. In non-life-threatening infections, cefazolin used in combination with gentamicin or ofloxacin may suffice. However, in most cases of serious infection, an extended-spectrum penicillin and an aminoglycoside or quinolone—with or without metronidazole—are necessary for complete coverage. Vancomycin usually is indicated when methicillin-resistant staphylococci are recovered.

For the comatose or immobilized patient, prevention of pressure sores emphasizes frequent turning, early mobilization, and avoidance of deep sedation or paralysis. Although automated “specialty beds” (see following) have largely supplanted their need, prophylactic use of thick or quilted foam (egg carton) or air-flotation mattresses should be considered for high-risk patients where these are not in use; they are effective preventative devices when used for short periods in patients exhibiting some spontaneous movement. Adjunctive measures include maintenance of an adequate tissue perfusion pressure (avoidance of hypotension), prevention of malnutrition, and elimination of tissue edema. When pressure sores develop, consultation with a wound care specialist for appropriate topical treatment can help prevent the devastating complications of cellulitis and systemic sepsis.

Specialty Beds

Air-fluidized, inflatable segment, low-air loss beds have gained great popularity in ICU practice, not only for their skin-sparing benefits but also for their ability to vary the distribution of pressure, to vary the body angle on a programmable schedule, to administer vibropercussion, to provide precise automated weights, and to facilitate cleanup, body positioning, and patient transfer. They most effectively prevent decubitus ulcers. Although extremely expensive, the latest generation of these instruments sufficiently extends capability to provide quality ICU care to make them the de facto equipment standard.

Beds with segmented air cushion capability can help in a variety of settings in which skin breakdown is well established or imminent. Soft beds of this type are particularly helpful for patients who must be positioned prone for extended periods, as they both cushion the contact points and facilitate the “flipping” process. Massively obese patients can benefit from “chair convertible beds,” which allow easy transitions between the supine and upright postures. Beds that allow the full range of body angulation can actively promote to transitions to the standing position. Although clinical experience with these innovations is currently limited, it seems reasonable to assume that such capability may facilitate mobilization during the recovery and rehabilitation phases of critical illness (Fig. 18-7).

Isolation Precautions

In a busy ICU, transfer of communicable pathogens is facilitated by the variety and multiplicity of the interactions that occur between patient, family, and caregivers. Certain principles of infection prevention in the individual patient are detailed in Chapter 26. Frequently, patients will require special attention to avoid transmitting infections to themselves or to others. To protect staff and fellow patients, the need for isolation should be
reconsidered frequently, and ICU nursing staff should be notified immediately of isolation plans. Visitors as well as staff must adhere to hygienic guidelines.

Several levels of protection are used in most ICUs (Table 18-4). Universal Precautions require at a minimum the use of gloves with any direct patient contact, including handling of body fluids (Table 18-4). They generally are recommended as the basal level of care for all patients in the ICU, but in reality, these standards are sometimes violated. Hand washing with proper technique and use of antiseptic foams (foam in-foam out) between patient contacts are mandatory when gloves are not used because they are among the most effective simple measures for avoiding spread of communicable pathogens. When used properly, antimicrobial gels, foams, and lotions are probably not quite as effective as proper hand scrubbing but have gained popularity as their convenience fosters compliance with prophylaxis guidelines. Using gloves does not entirely eliminate the need for hand washing as the warm, moist environment of the tight-fitting glove can serve as an effective incubator for small inocula of pathogens trapped beneath the fingernails, under the rings, and between the fingers. Relatively large inocula can then be transferred via fomites, coworkers, visitors, or subsequent ungloved contact with patients. It should be pointed out to poorly compliant staff that hand washing and use of gloves and cidal gels help to protect the caregiver from viral contamination, presumably reducing their own likelihood of colds and other transmissible diseases spread by skin contact. Any caregiver with a cold should wear a face mask.

**FIGURE 18-7. Position-variable bed and position-variable chair for the second (transitional) stage of ICU care.**

<table>
<thead>
<tr>
<th>Table 18-4. Categories of Protection and Isolation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Universal precautions for avoidance of contact with body fluids</td>
</tr>
</tbody>
</table>
Barrier gowns
Gloves
Mask
Eyewear
Face Shield

Isolation

Strict
Respiratory
Contact
Reverse

*Strict isolation* demands the donning of gowns, gloves, and masks whenever entering a patient's room and the removal of these items before exiting.

*Respiratory isolation* is observed in cases in which there is potential for airborne transmission of a dangerous, communicable pathogen. Well-fitting masks that meet a rigorous filtration standard high-efficiency particulate air (HEPA) are mandated or recommended in most hospitals for pathogens such as tuberculosis. Isolation rooms for respiratory pathogens are designed for one-way (outside room to inside room) airflow to prevent the dissemination of airborne pathogens to corridors and public areas.

*Contact isolation* requires the practitioner to take appropriate precautions (gloves, mask, and/or gown) when dealing with the affected area. Hand washing or gel usage should follow glove removal.

*Reverse isolation* is used for immunocompromised patients or at any time the clinician may transfer a communicable pathogen to the patient.

**Ambient Environment**

Modern ICUs acknowledge the need for critically ill patients to be cared for in a pleasant, temperature-controlled environment that encourages a normal sleep-wake cycle. Many units are required to provide visual access to the outdoors and appropriately ventilated and temperature-conditioned rooms. However, equipment and external temperatures during peak summer hours may cause even well-designed rooms to overheat. Such simple measures as drawing the shades during times of sunlight exposure and use of fans to improve air circulation can moderate any resulting discomfort.

Noise levels should be reduced whenever possible; gentle music intermittently provided via headphones or a bedside radio may comfort the conscious patient. It comes as no surprise that sleep quality is seriously compromised in the ICU (Fig. 18-8). Sedative-induced unrousability does not equal quality rest. Sleep architecture is fragmented, and even though total sleep time may be normal, sleep depth and phase content are not. The vast majority of ICU survivors relate sleep disruption as a serious problem—with as yet undetermined physiologic consequences. Earplugs should be considered for use during sleeping hours in unusually noisy rooms. In many instances, the volume of certain alarms can be muted safely at the bedside or “remoted” to the nursing station. Attempts to encourage a normal sleep-wake lighting and activity cycle may include “batching” of routine monitoring observations and patient manipulations as well as the systematic use of hypnotics, analgesics, and anxiolytics when appropriate. The importance of adequate high-quality natural sleep cannot be overrated. Providing adequate sleep markedly diminishes the incidence of disorientation and delirium. Hypnotics
that preserve relatively normal sleep architecture (such as zolpidem) are not without hazards but are probably underutilized in the high-stress ICU environment.

FIGURE 18-8. Contributors and consequences of sleep disruption in the ICU.

Comfort Measures
Anxiety and pain occur almost universally in the ICU setting. The skillful team blends the judicious use of anxiolytics with psychotropics, analgesics, physical measures, and concerted attempts to communicate. Vigilance to prevent or treat bladder and bowel distention, muscular skeletal discomfort, and pain arising from medication infusions (e.g., potassium, amphotericin, diazepam, bicarbonate, and erythromycin) are essential. Slowing the rate of administration, coadministration with a more swiftly flowing diluent, local use of lidocaine, hydrocortisone (e.g., for traditional amphotericin, 1 mg per mg of drug), and administration via a central vein are helpful strategies to minimize local pain. For certain medications (e.g., nonlipophilic or nonliposomal amphotericin), premedication with an antipyretic and antihistamine (e.g., diphenhydramine) can blunt the chills and fever that predictably accompany their administration.

Although benzodiazepines, propofol, dexmedetomidine, and opiates are used universally to reduce ongoing discomfort and anxiety, psychotropics such as quetiapine and olanzapine have been recognized as valuable adjuncts for some (see Chapter 10). Anxiety and pain reinforce each other, and early intervention can pay high dividends in aborting a spiraling pain—anxiety cycle (see Chapter 17). Such simple measures as variation of body position, back rubs, and heating pads may make an important difference. It has been shown that directing a stream of air over the face (using a fan) may reduce the sense of dyspnea, even in an intubated, mechanically ventilated patient.

Gastrointestinal Care
Impairment of gastrointestinal motility occurs frequently in critically ill patients, even in the absence of primary gastrointestinal disease. Prolonged abstinence from oral intake, dehydration, nasogastric suctioning, bed rest, opiates, and sedatives slow the gastrointestinal motility, especially in elderly patients. Simultaneously, air
swallowing and/or fixed-rate enteral feedings encourage abdominal distention that might impair diaphragmatic excursion. On the other hand, mucosal atrophy, edema of the bowel wall, antibiotics, and alterations of the native gut flora encourage malabsorption and diarrhea. Strategies to cope with these disturbances emphasize mobilization and the institution of oral intake as soon as feasible. Enteral feedings given at well-tolerated rates generally are preferred to parenteral nutrition. When feasible to use, bedside commodes are preferred to bedpans by many patients. Appropriate hydration, stool softeners, bulk-forming agents, gentle enemas, laxatives, motility stimulants (e.g., metoclopramide, erythromycin, enteral naloxone, and low-dose enteral physostigmine), and manual disimpaction are helpful options for problematic patients.

Copious diarrhea is a difficult management problem that carries the potential for nutritional depletion, electrolyte disturbances, and skin maceration (see Chapter 16). Ointments and coverings serve as an effective barrier when skin breakdown is imminent. Tests for detecting Clostridium difficile should be ordered, whether or not the patient has received antibiotics recently. Although not applicable for some situations, fecal drainage systems often work well, but frequently leak, and may be difficult to remove without spillage or tissue trauma. When diarrhea is profuse and thin, rectal tubes may be inserted for brief periods. To avoid serious complications because of erosion of the rectal mucosa, the tube should be removed periodically. Generally speaking, balloon inflation is inadvisable.

**Bladder Care**

Although invaluable for collecting and monitoring urinary output, Foley catheters should not be viewed as innocuous or inserted merely as a convenience. Intermittently catheterizing the bladder via a straight catheter and using an external collection apparatus are useful options when they are feasible to use and continuous urometry is not required. In the face of oliguria, a dysfunctional or clogged Foley catheter should be irrigated and/or replaced.

**Dressing and Wound Care**

Dressings around central lines and arterial catheters should be changed every other day unless required earlier. Transparent plastic windows in the specialized dressing placed over the catheter allow the skin puncture site to be monitored but are inappropriate if there is ongoing oozing of blood. No dressing should be allowed to remain soaked in wound drainage (blood, serum, pus). Communication with the nursing staff will enable the interested physician to examine the wound at the time that it is scheduled for exposure, obviating unnecessary dressing changes.

**Transportation Issues**

Transportation of the critically ill patient to a site outside the ICU tends to be a complicated and somewhat hazardous process that requires coordination among multiple caregivers. Patients requiring studies outside the ICU (most commonly for imaging studies and interventional radiology) must be well monitored, and all vital life-support systems must remain functional in transit. Emergency drugs and supplies should accompany the patient. Available transport monitors allow display of all important variables tracked at the bedside. As a rule, at least one ICU nurse is needed to observe the patient, to monitor cardiorespiratory function, and to intervene rapidly if difficulty arises. Two or more additional persons generally are required to maintain appropriate ventilation and move the bed, pumps, and ancillary equipment. Consequently, the nursing staff must know as early as possible about the need for and the time of the intended transport.

Because of the considerable risk and resource commitment, it is wise to consolidate diagnostic imaging and interventions that take place outside the ICU whenever feasible to do so. Sequential radiographic procedures should take place during the same session, whenever possible; it is not unreasonable to conduct CT scans in a predetermined
exploratory sequence during the same transport episode when the patient is critically ill and several diagnostic possibilities are at hand. To judge the wisdom of proceeding to the next step, the physician must be available to make the appropriate decision to proceed with, extend, or abort the planned studies.

Unstable patients are not good candidates for transport, especially when extended elevator and hallway exposure are required. Stable patients can be manually ventilated with the help of oximetry and cardiovascular monitoring. A minitrial of manual ventilation adequacy should be conducted at the bedside for several minutes before the actual move is attempted. Those more seriously ill may require a specialized transport ventilator capable of maintaining the required ventilatory pattern.

With modern drainage systems, thoracostomy (chest) tubes present little difficulty in transport if no suction is required to keep the lung adequately inflated. If a mobile suction system is not available for patients who are suction dependent (e.g., those with large bronchopleural fistulae), a water seal should be attempted at the bedside for a duration similar to that projected for the transport before its execution during the minitrial of transport ventilation—manual or automated. Prior arrangements should be made to reestablish suction drainage at the remote site.

**Gastrointestinal Ulcer Prophylaxis**

Before the availability of selective histamine receptor antagonists, proton pump inhibitors of gastric acid production, early enteral nutrition, and sucralfate, gastrointestinal bleeding that resulted from stress ulceration presented a distressing and occasionally a life-threatening problem (see Chapter 37). Fortunately, these complications currently are encountered much less frequently. Patients receiving effective enteral feeding seldom experience erosive stress ulcers and may not require special measures to prevent them. Whether acid inhibition encourages the overgrowth of bacteria within the stomach and thereby predisposes patients to aspiration pneumonia remains an unsettled issue.

**Leg-Clotting Prophylaxis**

Trauma, recent surgery, sepsis, dehydration, immobility, venostasis, procoagulants, clotting factor aberrations, and a variety of other predisposing factors accentuate the tendency to form lower extremity clots. Prophylactic interventions—both mechanical and pharmacologic—to prevent venous thrombosis in the lower extremities are indicated in most patients placed on bed rest in the ICU setting. Support stockings are used for mobile patients but have little place in the bedridden. High-risk patients are usually given subcutaneous heparin or low molecular weight heparin unless there is an overriding contraindication (e.g., ongoing blood loss, heparin-induced thrombocytopenia [HIT], intracerebral hemorrhage, or coexisting risk of bleeding complication) (see Chapter 23). Intermittent leg compressive devices (e.g., “pneumo boots” and “foot pumps”) are more effective than are support stockings and do not carry the risks of anticoagulants (Fig. 18-9). They may, however, be uncomfortable for alert patients or may result in skin breakdown in poorly nourished, edematous patients with circulatory insufficiency. Patients with known lower extremity clot and a contraindication to unfractionated heparin and its low molecular weight derivatives may be offered a **removable** intra-vena caval filter if a non-heparin-based anticoagulant (e.g., lepirudin or argatroban) is not advisable.

**Respiratory Care**

Few hospital services are as valuable to patient care as respiratory therapy (RT). However, RT is often ordered indiscriminately at substantial discomfort, morbidity, and financial cost. Respiratory care services are now under pressure to become optimally cost-effective as hospitals face financial constraints imposed by prospective payment and reimbursement limitations. Therapist-driven protocols for ventilator management and other RT
and generally improve care delivery. Nonetheless, understanding the indications and contraindications for RT procedures remains important for appropriate patient management (Table 18-5).

FIGURE 18-9. Automated periodic calf compression (right leg) and foot pump (left foot) to help prevent deep venous thrombosis during sustained bed rest.

### Table 18-5. Respiratory Care Services

| Assisted coughing |
| Deep breathing |
| Incentive spirometry |
| Noninvasive ventilation |
| CPAP/Bi-PAP |
| Nasal high flow |
| Bronchodilator administration |
| Invasive mechanical ventilation |
| Chest percussion and postural drainage |
| Airway suctioning and hygiene |
| Procedural assistance (e.g., bronchoscopy) |
| CPR and rapid response teams |

Respiratory Care Procedures
Assisted Coughing

Encouraging productive coughing is among the most effective services a therapist provides. Bronchodilator secretion mobility can be encouraged by hydration, bronchodilators, and guaifenesin. Many patients can be assisted by timing the session to coordinate with alertness and scheduled analgesia dosing or by using pillows to splint any painful areas of the abdomen or chest. Exhalation pressure can be increased in patients with quadriplegia by abdominal compression coordinated with the patient’s spontaneous expulsive efforts. Mechanical devices are available to evoke an effective cough by slowly pressurizing a deep breath and quickly depressurizing the air column.

Deep Breathing

Healthy individuals spontaneously take breaths that are two to three times greater than the average tidal depth multiple times per hour. Sighs to volumes approaching total lung capacity (TLC) occur less often but are by no means unusual. Animated, uninterrupted speech also requires deep breathing. Many influences, including sedatives, coma, and thoracoabdominal surgery, abolish this pattern, encouraging atelectasis and secretion retention. Deep inspirations or manual hyperinflations not only combat atelectasis but also deliver air distal to the secretions, thereby improving cough effectiveness and occasionally triggering an effort reflexly. Useful deep breathing starts from FRC, ends at TLC, and sustains inflation at a high lung volume for several seconds. Nonexpulsive maneuvers that encourage exhalation rather than inhalation actually may be counterproductive.

Upright positioning is perhaps the most effective means of sustaining a higher lung volume in the nonintubated patient. In moving from the supine to the erect posture, a normal lung may experience a 500-1,000-mL increase in volume, a change equivalent to 5 to 10 cm H₂O PEEP. Changing the position of patients with unilateral disease may notably affect both gas exchange and secretion clearance. Turning is especially important for patients immobilized by trauma, sedation, or paralysis.

Incentive Spirometry, CPAP, and Bilevel Airway Pressure

Several methods are used to encourage sustained deep breathing in nonintubated patients. An incentive spirometer is a device that gives the patient a visual indication of whether the inhalation effort approaches the targeted volume. Despite their potential utility, only the highly motivated patient can cooperate fully in their use, and lung volume falls to near baseline immediately after the exercise. Interestingly, nasal high-flow oxygen tends to encourage deeper breathing and provides sustained low-level upper airway pressure (see Chapter 8).

Noninvasive ventilation (e.g., bilevel positive airway pressure [Bi-PAP]) and continuous positive airway pressure (CPAP; see Chapter 7) are now an entrenched part of respiratory care. Intermittent use of CPAP or Bi-PAP applied by a well-sealed mask often succeeds in improving gas exchange. One primary advantage over incentive spirometry is that end-expiratory increments in lung volume are sustained, improving efficacy of atelectasis reversal and prophylaxis.

Bronchodilator Administration

A nebulizer used with a mouthpiece or simple face mask can be used to deposit a small amount of drug on the airways if no other method is feasible. Metered-dose canisters do not deliver the intended dose unless the patient coordinates the puff with the breathing cycle or a spacing chamber attachment is used. The latter is essential for marginally cooperative or maladroit-hospitalized patients, and efficacy may be comparable to the compressor-driven method when a sufficient number of puffs are given through a spacing inhalation chamber. If the patient is mechanically ventilated, medication can be delivered through the inspiratory limb of the circuit. This can be accomplished either with a traditional “wet” nebulizer
or by insufflation of multiple puffs from a metered-dose unit timed with the inflation phase.

**Chest Percussion and Postural Drainage**

The objectives of percussion and postural drainage (chest physiotherapy [CPT]) are to dislodge the secretions from peripheral airways, to mechanically disrupt and mobilize thickened sputum, and perhaps to encourage gas to migrate behind secretion plugs so as to improve cough effectiveness. In the traditional method, vibration or hand percussion of the involved region is performed for 5 to 15 minutes, optimally with the involved segment(s) in the position of best gravitational drainage and with the postural drainage position maintained for an additional 5 to 15 minutes afterward. Bronchodilator administration should precede CPT, and deep breathing and coughing should be encouraged before, during, and after the 10 to 15 minutes of optimal positioning. As already noted, some specialty beds can provide automated vibropercussion of variable frequency and amplitude, and devices are now available to vibrate the air column. These innovations have all but supplanted the manual chest percussion for the intubated patient. For well-selected patients with diffuse airway disease and copious secretions (e.g., cystic fibrosis or bronchiectasis), a vibrating inflatable vest powered by a compressor and usually operated in an upright position may be effective as an aid in secretion clearance.

These resource-intensive and intrusive physiotherapy methods are best reserved for patients with unusually copious secretions who can safely undergo them and empirically demonstrate unequivocal benefit. Patients most likely to improve after treatment are those who retain secretions because of impaired clearance mechanics (e.g., airflow obstruction, neuromuscular weakness, or postoperative pain). Although CPT may benefit patients with acute lobar atelectasis and those unable to clear secretions, patients with a vigorous cough experience little added benefit. CPT is appropriate to consider in the ICU setting, provided hypotension, cardiac arrhythmias or ischemia, thoracic incisions, tubes, position limitation, rib fractures, or other mechanical impediments do not contraindicate its use.

**Airway Suctioning**

Nasotracheal suctioning in the nonintubated patient serves two purposes: (1) to stimulate the coughing efforts that bring distal secretions to more proximal airways and (2) to aspirate secretions from the central bronchi. Traumatic and uncomfortable, the airway must be suctioned sparingly, especially in patients with heart disease; associated vagal stimulation and hypoxemia can be arrhythmogenic. Inherently less effective than a productive cough, tracheal suctioning should be performed only when a sputum specimen cannot otherwise be obtained or when ventilation or oxygenation is compromised by secretions retained in the central airways. A blindly placed suction catheter usually reaches the lower trachea or right main bronchus and recovers sputum from the more distal airways only if cough propels the sputum forward. Soft nasal “trumpets” facilitate retropharyngeal clearance and act as guiding channels to the glottic aperture (see Chapter 6). Shaped catheters favor cannulation of the left main bronchus. For mechanically ventilated patients, closed systems allow the simultaneous provision of PEEP.

Proper technique emphasizes hygienic but not rigidly sterile precautions. “Preoxygenation” is first accomplished by several deep inflations of pure oxygen. After the trachea is entered, the catheter is advanced 4 to 5 in. and then is withdrawn as intermittent suction is applied and released for no longer than 5 seconds. Several “hyperinflations” of oxygen are given before resuming the usual ventilatory pattern.

**Methods of Oxygen Administration**

Most patients admitted to the ICU will require supplementation of inspired oxygen. To apply this vital treatment most effectively, the clinician must be aware of the advantages, drawbacks, and limitations of each available technique (Table 18-6).
Nasal Cannulae (Prongs) and Nasal Catheters

Nasal prongs are perhaps the best choice for most applications requiring moderate oxygen supplementation. Continuous flow fills the nasopharynx and oropharynx with oxygen. These reservoirs empty into the lungs during each tidal breath, even when breathing occurs through a widely open mouth. One of the two prongs can be taped flat (or cut off and the hole sealed) without a notable change in FiO\textsubscript{2}, allowing effective supplementation to continue despite the presence of an occlusive nasogastric tube, nasotracheal suction catheter, or bronchoscope in the other nostril. Nasal prongs allow an uninterrupted flow of oxygen while eating or expectorating and during procedures involving the oropharynx (such as suctioning and orotracheal intubation). Prongs taped in place reliably deliver oxygen to patients who tend to remove their face masks.

### Table 18-6. Methods of Oxygen Administration

<table>
<thead>
<tr>
<th>NASAL CANNULAE AND CATHETERS</th>
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</thead>
<tbody>
<tr>
<td>Conventional at low-moderate flows (2-10 L/min)</td>
</tr>
<tr>
<td>High-flow nasal catheter (30-60 L/min)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>MASKS</th>
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</thead>
<tbody>
<tr>
<td>Open</td>
</tr>
<tr>
<td>Simple</td>
</tr>
<tr>
<td>Venturi</td>
</tr>
<tr>
<td>Partial rebreather</td>
</tr>
<tr>
<td>Nonrebreather</td>
</tr>
<tr>
<td>Face trough</td>
</tr>
<tr>
<td>Tracheostomy dome</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Semiclosed</th>
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<tbody>
<tr>
<td>Noninvasive CPAP or NIV (Bi-Pap)</td>
</tr>
<tr>
<td>Full face mask</td>
</tr>
<tr>
<td>Nasal mask</td>
</tr>
<tr>
<td>Helmet</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>SEAMED AIRWAY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotracheal tube</td>
</tr>
<tr>
<td>Tracheostomy</td>
</tr>
</tbody>
</table>

With the exception of high-flow nasal oxygen (HFNO), which is purpose-designed for temporary use in the most tenuous patients and offers unique features that aid ventilation (see Chapters 7 and 10), rates of nasal oxygen administration usually vary from 0.5 to 8 L/min, depending on the clinical situation, duration of application,
patency of the nasal canals, and size of the patient. At a fixed oxygen flow rate, the FiO\(_2\) achieved depends on minute ventilation. Therefore, a “low flow” rate of 2 L/min may correspond to a low or moderately high FiO\(_2\), depending on whether it is diluted with a large or small quantity of ambient air. For an average patient, 0.40 approximates the upper limit of FiO\(_2\) achievable by this method.

A jet of dry oxygen desiccates the nasal mucosa, encourages surface bleeding, and may invoke pain in the paranasal sinuses at high flow rates. Oxygen must be humidified if given faster than 4 L/min with two prongs or 2 L/min with one prong. A non-petroleum-based lubricating jelly applied to each nostril is a useful prophylactic measure against local irritation.

A nasal catheter is a single-perforated plastic tube advanced behind the soft palate. Somewhat more secure than nasal prongs but used much less frequently, catheters deliver similar concentrations of oxygen. They are less popular than prongs because of greater irritation to nasal tissues, because location must be checked frequently, and because the catheter must be alternated between the nostrils every 8 hours. Oxygen-conserving devices that inject gas only during inspiration have been introduced successfully to outpatient practice. Whether similar units will prove cost-effective in the hospital setting has not yet been determined.

Face Masks

Face masks can provide higher oxygen concentrations than are available with open tents and nasal devices but are inherently uncomfortable and less stable than other methods that deliver similar inspired fractions of oxygen (Fig. 18-10). Masks must be removed when eating and expectorating, allowing the oxygen concentration to fall during these activities. Unrestrained patients often dislodge them when agitated, dyspneic, or sleeping.

There are five common types of face masks: simple, partial rebreathing, nonrebreathing, open tent, and Venturi. Simple masks have an oxygen inlet at the base and 1.5-cm-diameter holes at the sides to allow unimpeded exhalation. Because the peak inspiratory flow rate usually exceeds the set inflow rate of oxygen, room air is entrained around the mask and through the side holes. Therefore, the FiO\(_2\) actually delivered depends not only on the oxygen flow rate but also on the patient's tidal volume and inspiratory flow pattern. In an “average” patient, the oxygen percentage delivered by a simple mask varies from approximately 35% at 6 L/min to 55% at 10 L/min. At low flow rates, CO\(_2\) can collect in the mask, effectively adding dead space and increasing the work of breathing. Venturi masks provide a concentration of oxygen no higher than that specified. Oxygen is directed into a jet that entrains room air to flood the facial area with a gas mixture of fixed oxygen concentration. If the patient's peak inspiratory flow rate does not exceed the combined flow of the oxygen-air mixture, the FiO\(_2\) will be the nominal value, provided the mask fits snugly. Venturi masks are available to deliver selected oxygen percentages varying from 24% to 50% and have all but replaced simple masks in routine ICU practice. Some masks allow rapid switching of the delivered concentration by adjustment of a collar selector, which changes the entrainment ratio.
FIGURE 18-10. Four types of oxygen delivery devices for patients requiring no ventilatory assistance.

The structure of the partial rebreather (reservoir) mask is virtually identical to the simple mask, but oxygen flows continuously into a collapsible reservoir bag attached to the base. If the mask is well sealed around its edges, the patient inspires from the bag when demand exceeds the constant line supply. Peak efforts draw less air from the room and a higher FiO\(_2\) is achieved. The reservoir must be kept well filled; if the bag is allowed to collapse, the partial rebreather converts to a simple mask. Although these masks may make more efficient use of oxygen, the highest FiO\(_2\) usually achievable with this device is approximately 0.70.

Nonrebreather masks are identical to partial rebreather masks, except for two sets of one-way valves. One valve set is placed between the reservoir and the breathing chamber so that exhaled gas must exit through the side ports or around the mask. The second valve set seals one or both side ports during inspiration in such a fashion that nearly all inhaled gas is drawn directly from the oxygen reservoir. With a well-sealed and tightly fitting mask, inspired oxygen concentrations exceeding 80% can be delivered. Oxygen inflow must be high enough to prevent collapse of the reservoir bag. If collapse occurs, oxygen delivery rate would be insufficient to meet ventilation requirements, causing the patient to struggle against the one-way valves to entrain additional room air. Masks without a safety release mechanism could conceivably allow a weak or restrained patient to suffocate. Therefore, patients on nonrebreather masks should remain under direct observation. High-flow nebulizer attachments (e.g., Misty-Ox) can maintain nearly unlimited flows of humidified supplemental oxygen to a modified, loose-fitting mask.

Open-face troughs can deliver either oxygen or mist and can serve a useful purpose for patients who will not tolerate tight-fitting masks or nasal cannulae. They allow the patient to communicate and expectorate easily but impede eating. The FiO\(_2\) varies widely with the set flow rate, tent position, and minute ventilation. Even when complemented adjunctively by nasal prongs, inspired oxygen fractions cannot be boosted above approximately 0.6 because of entrainment of ambient air. With all the methods of
oxygen delivery discussed thus far, \( \text{FiO}_2 \) can vary depending on the patient's breathing pattern. In certain clinical situations, such as decompensated chronic obstructive pulmonary disease (COPD) with \( \text{CO}_2 \) retention, more precise control of \( \text{FiO}_2 \) may be desired.

**Endotracheal Tubes**

Any inspired fraction of oxygen can be delivered when a cuffed endotracheal tube prevents access to room air. If the patient is not connected to a ventilator circuit, humidified gas is administered by either a T-piece adapter or a tracheostomy tent or dome. If no “tail” (wide-bore tubing) is attached to the T-piece adapter, the concentration of oxygen delivered will be less than that in the afferent tubing because of dilution by room air during inspiration. A length of tubing attached downstream from the endotracheal tube orifice provides an inspiratory reservoir to counteract this effect without adding dead space. The length needed depends on the source flow rate and the patient's peak flow demand.

A tracheostomy mask is a small, open-domed hood that creates a tentlike area over the tracheostomy orifice. Some room air entrainment occurs, tending to reduce both humidity and \( \text{FiO}_2 \). The latter usually can be overcome by increasing the \( \text{FiO}_2 \). The tracheostomy mask is less unwieldy than a T-piece and does not produce traction on the tracheostomy tube.

**Humidification**

During spontaneous normal breathing, humidification is accomplished by the well-vascularized mucosa of the nasal and oral passages. At normal rates of breathing, the nose is an efficient conditioner of air, filtering out particles greater than 10 \( \mu \text{m} \) in size and completing the warming and humidifying process before gas enters the larynx. The mouth is somewhat less effective, especially at high minute ventilation. If humidification is not completed in the upper airway, water must be drawn from the tracheobronchial mucosa, causing desiccation, impaired mucociliary clearance, and thickened sputum.

Unlike ambient air (which is, on average for most locales, 50% saturated), medical gases contain no water vapor, so the entire amount must be supplied. Unhumidified gas rapidly dries the nasal and oral mucosae, especially when oxygen is being administered. If the upper airway is bypassed, as by endotracheal intubation, drying of the sensitive lower tract occurs, with the attendant risk of infection and ventilatory impairment. The object of external humidification is to provide gas containing acceptable amounts of water vapor to the respiratory tract. Gas introduced at the tracheal level must be fully prewarmed and saturated. If the upper tract is not bypassed, humidity and temperature similar to those of ambient air usually suffice.

Without the upper airway bypassed, low flow rates of oxygen (e.g., up to 3 L by nasal prongs) mix with sufficient ambient air to preclude the need for humidification, unless the ambient environment is exceptionally dry. External humidification is required with higher flow rates by prongs and with masks that deliver moderate to high oxygen concentrations. Humidification is required in most patients receiving mask Bi-PAP as well, especially as many breathe at elevated levels of minute ventilation, with high concentrations of dry oxygen through an open mouth. For intubated patients, humidification can be accomplished either by disposable heat and moisture exchangers (see following) or by units that fully saturate the inspired airstream as they warm it to near body temperatures (32°C to 37°C) (see Chapter 7). Heated wire circuits often are used to maintain a nearly uniform temperature within the inspiratory tubing and thereby prevent airstream cooling and excessive “rain out” of the supersaturated water vapor.

In recent years, disposable, lightweight hygroscopic filters placed in the common limb of the ventilator circuit have supplanted sophisticated mechanical humidifiers for many less demanding applications. This heat and moisture exchanger (HME, or artificial nose) is designed to recover much of the exhaled moisture that otherwise
would be lost to the atmosphere, releasing it to the inspired gas of the next breath. Such units economically serve the needs of patients without severe illness who have adequate breathing reserve and modest ventilation requirements. However, because they clog rather easily, impose dead space, increase airway resistance, and exhibit declining efficiency at high levels of ventilation, hygroscopic filters are less well suited to some severely ill patients and those who have a high secretion burden.

**SUGGESTED READINGS**


Peitz GJ, Balas MC, Olsen KM, Pun BT, Ely EW. Top 10 myths regarding sedation and delirium in the ICU.

Schmidt UH, Knecht L, MacIntyre NR. Should early mobilization be routine in mechanically ventilated patients? *Respir Care.* 2016;61(6):867-875.


Chapter 19
Quality Improvement and Cost Control

• Key Points

1. High quality, cost-efficient care requires dedicated, open-minded, and well-trained ICU leaders who are provided with accurate performance data and the power to establish unit policy.

2. Critical care is best delivered by critical care-trained physicians and nurse practitioners who understand physiology; communicate effectively; use well-reasoned, standardized care plans; and employ adaptive judgment.

3. The entire ICU staff must work as a team toward well-defined, patient-directed goals. Daily multidisciplinary rounds are an essential feature of quality care and team building.

4. Patient charges for critical care services bear little relationship to actual costs because of high inflexible “overhead,” inherent excess capacity of the ICU, expensive and rarely needed services, and arbitrary price fixing by hospitals and payers.

5. Nursing labor costs constitute the bulk of ICU spending.

6. Wise use of diagnostic laboratory, radiology, and pharmacy services can reduce costs. Protocols or pathways for using these services must be crafted individually to meet the needs of individual ICU and patient populations.

Running an ICU requires managing three inextricably linked factors: quality of care, effectiveness, and cost control. Although increasing resource utilization does not necessarily lead to improved quality, inefficiency almost always detracts. Conversely, improving quality reduces both resource utilization and costs as it improves efficiency. Typically, such savings are achieved by (1) reducing length of stay, (2) preventing complications and readmissions, (3) limiting ineffective or excessive care, (4) reducing staff turnover, and (5) committing as a team to optimal effort for patient- and family-centered care.

BUILDING QUALITY

ICU Leadership

Quality care begins with respected, competent, and experienced critical care-trained physician and nurse leaders who are devoted to providing first-rate care. Although ICUs essentially always have a designated nursing leader, surprisingly less than half of ICUs have a dedicated medical director. Almost as bad as not having a director is having one who is a “figurehead” uninvolved in the daily workings of the unit. The director must be easily reached and should play a central role in smoothing the admission, discharge, and transfer processes; in establishing standard policies, procedures, and protocols; and in assembling a competent, effective, and efficient staff. Although it is a tall task, it helps if the leaders serve on hospital committees that have a large impact on ICU practice, such as the pharmacy, resuscitation, and laboratory services groups. To improve quality and control costs, ICU leaders must be provided with accurate performance data, remain open to new solutions, and have the authority to change practice by establishing policy. Ideally, the medical and nursing directors of all ICUs in a hospital meet regularly and work together to implement the best practices.
Excellence is defined as the quality of being exceptionally good or possessing a special quality that confers superiority. Excellent physicians achieve a level of mastery in communication and interpersonal skills, professionalism, and humanism and successfully navigate complexities of the health care system. These individuals are exemplary with respect to diagnostic skill, knowledge, and scholarly approach to clinical practice. They exhibit passion for patient care and are role models for trainees.

Today, physicians spend less time at the bedside with patients and families because they strive for greater throughput and efficiency and are obligated to satisfy greater requirements for documentation so as to satisfy reimbursement requirements and avoid litigation. Often harried, physicians have less time to dedicate to scholarship and professional renewal. Patient care is sometimes splintered among various specialists who seemed to be addressing individual organ systems rather than the whole patient. Such barriers to excellence may be magnified in the critical care environment. Organizational changes that may help reverse the trend toward increasing time pressure and depersonalization in critical care include expanding the number of available providers and employing technological innovations that facilitate humanistic interactions with fellow caregivers, patients, and families.

**Burnout**

Because of increased expectations, longer hours, and a relative lack of community support in the workplace, the amount of work-related stress has increased over the last few decades. As a result, burnout syndrome has become a common worldwide phenomenon, especially among members of high-stress professions such as firefighters, police officers, teachers, and health care professionals. Compared with all high school graduates, physicians are more likely to experience burnout.

Burnout is triggered by discrepancies between the expectations and ideals of the employee and the requirements of his or her position. Symptoms of burnout typically develop gradually. In the initial stages of the condition, individuals feel emotional stress and job-related disillusion. They subsequently lose the ability to adapt to the work environment and display negative attitudes toward job, coworkers, and patients. Three classic symptoms of burnout have been identified. These are exhaustion, depersonalization, and reduced personal accomplishment.

Exhaustion is generalized fatigue related to devoting excessive time and effort to a task or project with unsatisfying returns. An example may be the need to continue demanding care for a patient with very poor prognosis. Depersonalization is a distant or indifferent attitude toward work. It presents as callous and cynical behaviors or interacting with colleagues or patients in an impersonal manner. Depersonalization may be expressed as unprofessional comments directed toward coworkers, blaming patients themselves for their medical problems, or the inability to express empathy or grief when a patient dies. Reduced personal accomplishment is the tendency to negatively evaluate the worth of the work, feeling insufficient regarding ability to perform the job, and poor professional self-esteem.

Approximately 25% to 33% of critical care nurses manifest symptoms of burnout, and up to very high percentages have at least one of the three classic symptoms. The relative shortage of critical care physicians and the demands for overnight ICU coverage have increased burnout among intensivists. Compared with other types of physicians, critical care physicians have the highest prevalence of burnout, followed closely by emergency medicine physicians. In general, organizational factors related to burnout include increasing workload, lack of control over the work environment, insufficient rewards, and breakdown in the sense of work community. Burnout in critical care health care professionals may result in posttraumatic stress disorder (PTSD), alcohol abuse, and even suicidal ideation. PTSD is manifest by intrusion, avoidance, negative alterations in
cognition and mood, and marked changes in arousability and reactivity.

Strategies to prevent and treat burnout focus on enhancing the ICU environment and helping the individual cope with the stresses encountered. Improvement in work environment is related to skilled communication, true collaboration, effective decision-making, appropriate staffing, meaningful recognition, and authentic leadership. Building individual resiliency requires adequate self-care, adequate rest, spiritual practices, exercise, meditation, and hobbies outside the work environment. Establishing a work-life balance and employing time management skills and stress reduction measures may also reduce the risk of burnout.

**The Intensivist**

Critical care is not just internal medicine, pediatrics, or general surgery plus a few procedural skills. The ICU contends with a wide range of potentially lethal problems and uses sophisticated technology to which the primary care provider typically has limited exposure. Because of the rapid pace of illness and events in the ICU, decisions must be made quickly, often using incomplete information. The non-ICU practitioner typically has little experience with the high-stakes uncertainty that characterizes this setting.

Ideally, physicians working in ICUs should be critical care trained and readily available, yet less than 5% of ICUs have a senior physician present around the clock, and less than one third of all ICUs have continuous “resident” level coverage. More striking is the fact that fewer than 20% of hospitals have a critical care-trained physician on site continuously even during daylight hours. This situation is unfortunate because numerous studies indicate that establishing a “closed unit,” where patients are cared for by a critical care physician, reduces the length of stay, mortality, and costs. There are several potential reasons for improved outcomes with intensivist staffing. ICU physicians are more likely to be immediately available, without the distraction of a busy clinic or operating room schedule. The advantages of dedicated intensivists are eroded when physicians are not physically present, for example, when they provide care in geographically separated units. Benefit may also result from the fact that intensivists have a body of experience that allows them to anticipate and preempt serious problems before they become fatal or costly. For example, to an intensivist at the bedside, subtle increases in airway pressure and modest declines in saturation and blood pressure are likely to signal an early pneumothorax that can be successfully treated long before it results in serious injury. An off-site physician is less likely to appreciate and promptly act upon these very same findings. The presence of a dedicated intensivist also increases consistency of care and compliance with recommended practices. Examples abound: when no standards exist, deep venous thrombosis prophylaxis, fluid resuscitation for septic shock, glucose control, nutrition, and lung protective mechanical ventilation may be inconsistent in method and application. When a different method is used for every patient, it is likely that the therapy will be overlooked for some patients and suboptimal in others. Despite fierce arguments for physician autonomy and “customization” of care, usually there is a best way to begin treating the typical patient. Reducing unnecessary variation contributes to improved quality. Furthermore, knowing which treatments have succeeded or failed in a given patient leads to more efficient and less costly care.

In an era in which patient turnover is rapid, and staff changes are frequent, well-crafted policies, protocols, and checklists are essential to consistent care. Variability in care can be magnified in teaching hospitals where trainee duty hours are tightly constrained, necessitating frequent handoffs. Another potential advantage of the on-site critical care physician is that he or she is less likely to summon multiple consultants. Care is inefficient, costly, and potentially dangerous when a physician, especially one off-site, “practices” using multiple consultants. In this model, each consultant responds at a pace dictated by his or her schedule, and the communication between the consultants, the primary physician, and the family is often suboptimal. The intensivist is the best person to adjudicate and coordinate the consultant recommendations and to communicate
with the family and with the physicians who will provide care after ICU discharge. Without effective coordination, it is possible for numerous, often redundant, diagnostic tests to be ordered as subspecialists attempt to justify their involvement by searching for evermore obscure conditions. Even worse situations develop when the therapeutic goals of consultants are at odds or when one consultant is oblivious to the thoughts of another.

Perhaps no one is better attuned to the potential for and limitations of the ICU than the intensivist, the person most qualified to identify patients who cannot benefit from ICU care because they either are not sufficiently ill or are unsalvageable. Patients at low risk of death or complications tie up needed beds and are more likely to experience an adverse event as a result of ICU admission than they are to experience benefit. Hence, “low-risk admissions” should be avoided. Likewise, moribund patients are not well served by ICU admission, where they occupy beds that could be used for more salvageable candidates, may suffer isolation from family and friends, are exposed to nosocomial hazards, and pay a high financial price. Even with all the difficulty in determining what “futile” care is, reasonable limits can be developed on a case-by-case basis. The intensivist, strongly aided and informed by nursing input, is the best person to help the patient and family develop these boundaries by having honest, open, and recurring discussions of expectations. Recurring discussions with the patient and family are important to ensure maintenance of common goals, as attitudes often change in response to evolving illness. Such consultations often require 30 to 60 min/patient each day, a time requirement that few physicians with responsibilities outside the ICU can manage. Beginning routine family discussions early in the ICU stay makes later meetings when weighty decisions must be made much less daunting. This plan of communication has other benefits: patient and family satisfaction is enhanced by communication with fewer physicians delivering a consistent message.

The role of the “hospitalist” in the care of the critically ill patient remains ill defined. Although one would expect that a hospitalist providing around-the-clock care would be superior to the absence of an in-house physician, the training, experience, and scope of responsibilities of the hospitalists are heterogeneous. For example, many hospitalists are internists with no formal critical care training who have chosen to limit their practice to inpatient medicine. It is also not clear if a physician providing coverage for many patients throughout the hospital provides the same level of attentive care as does a physician dedicated to the ICU.

When well implemented, telemedicine fills an important gap in delivering sophisticated specialty care, especially for otherwise understaffed care environments. However, the eventual role of the “telephysician” remains uncertain, and the implementation of a telemedicine program is quite expensive. In practice settings lacking any organized critical care presence, the addition of telemedicine oversight is likely to produce significant improvements in care delivery. However, in settings where critical care physicians are already present during the day, outcome improvement has not been convincingly demonstrated. Interestingly, it is not clear if the benefits of telemedicine come from the oversight function of the service or from establishing the standardized methods of dealing with common issues.

Undoubtedly, a well-trained and experienced on-site intensivist is the best person to care for critically ill patients and orchestrate the involvement of necessary consultants. Unfortunately, this ideal model is currently impractical because even in large tertiary care centers, there are rarely sufficient numbers of critical care physicians to provide in-house, 24-hour-a-day coverage.

**Advanced Practice Providers**

One of the most pressing challenges facing the critical care community is our ability to provide high-quality care to all critically ill and injured patients. Effective solutions for high-acuity patients involve team care. Access to high-quality critical care may require creating new types and levels of critical care professionals who are able to
evaluate, prescribe, and perform procedures. Physician assistants and acute care nurse practitioners (ACNP) have seen an increasing role in first response to critical illness, patient stabilization tasks, patient admission, provision of time-sensitive treatments, and conduct of essential procedures. A well-trained ACNP serves as a unit lynchpin—a steady presence who educates, assures best practices as staff and residents rotate and change, and connects with families and providers at all levels. The effectiveness of these advanced practice providers has been demonstrated in a growing number of studies. Recent work demonstrates the high standard practiced by teams involving advanced practice providers with appropriate intensivist oversight. This expanded capability is increasingly important in order to maintain continuity of care for acutely ill patients in the face of strict limitations imposed on resident work hours.

Critical Care Nurses

Critical care nurses are the patient's lifeline and family's touchstone to the care delivery system. Today's nurses are being asked to do more highly technical, labor-intensive tasks with a greater level of independence than ever before. In this environment, making sure that nurses are not overburdened is as important as making sure that they are well educated and current in their training. Given the intensity of ICU activity, anytime a nurse is asked to care for more than two (sometimes more than one) critically ill patient(s), it is likely that less than ideal care is being delivered. When task saturation occurs, it is common for nurses to keep performing essential patient-centered work, but care of the family and documentation suffer. Although a heretical idea to some, lapses in documentation are usually unimportant, unless a critical event or adverse occurrence is inadequately described, leading to its repetition. Nonetheless, it is best to avoid any inconsistency in care or documentation by providing adequate staffing. To this end, bedside nurses, ICU leaders, and administrators must work together to ensure that the process of care is efficient. New programs and initiatives should be thoroughly vetted before implementation to make sure that additional work or documentation requirements do not detract from care of the patient or family. Good recent examples of “process of care” changes that imposed substantial burdens are institution of intensive glucose control, early mobilization programs, and continuous renal replacement therapy. Sometimes, seemingly trivial requirements carry significant work implications; for example, simply documenting that mouth care and repositioning have been done every few hours can be time intensive, especially if the system for documentation is inefficient.

ICU nurses are not interchangeable cogs in a large critical care machine. They develop specialized skills to serve the most common problems they see and become familiar with the policies, procedures, and layout of the unit in which they most often work. Simply not knowing where supplies or equipment are stored in an unfamiliar unit results in inefficiency and, in some cases, danger. In addition, the teamwork and camaraderie that develop among nurses who work consistently together provide physical and emotional support to complete the difficult tasks they are called upon to do. For these reasons, the use of temporary nurses or rotating nurses between ICUs of different disciplines should be discouraged.

Nursing excellence requires much more than a caring attitude, technical knowledge, and careful documentation; experience brings priceless insight, intuition, or judgment. Every savvy critical care physician knows the folly of not promptly responding to an experienced nurse who says “I'm not sure what's wrong, but the patient just doesn't look right.” Not only can one not buy experience, but it is also very expensive to retrain or orient a nurse to a new ICU; some have estimated costs at tens of thousands of dollars. Hence, it makes sense to do everything reasonably possible to retain quality nurses.

Although nurses certainly care about salary, benefits, and work hours, satisfaction at work is a much more important factor for staff stability. There are numerous ways to improve nurse's job satisfaction. The first and
probably the most important factor to enhance satisfaction is to treat nurses as the indispensible elements of a team providing care. Just like the copilot of an aircraft, nurses provide critical information and accomplish crucial tasks for successful mission completion. Airlines long ago recognized that an intimidating, unapproachable captain was a dangerous and divisive employee; the same is true of a dictatorial ICU physician who disregards a nurse’s ideas or observations. Although it is clear that one person (the attending physician) must make the key decisions, there is no room for paternalism, patronization, or dismissive attitudes. For satisfaction, but more importantly for patient safety, everyone caring for patients should understand the plans for care and must feel free to speak up when a course of action appears to be not working. Another method to promote staff satisfaction is to develop an environment where learning and teaching are valued and inquiry is welcomed. Conducting formal clinical trials or quality control projects helps establish an environment where questions are welcomed and a culture of discovery flourishes. Conducting regularly scheduled educational programs designed to answer the questions that arise during patient care is also valuable and vastly superior to an arbitrary or irrelevant schedule of topics. By having all members of the health care team present at educational sessions, the knowledge of the group is boosted, the stature of the presenter is enhanced, and, as a result, care improves.

Pharmacists, Nutritionists, and Physical and Occupational Therapists

The ICU pharmacist is pivotal for optimal patient outcomes and cost control. The role of pharmacists and methods to optimize pharmacotherapy are covered in detail in Table 19-1 and Chapter 15. Similarly, the ICU dietitian provides valuable guidance for nutritional requirements and is essential to help determine individual needs and navigate the dizzying variety of products available. Although clearly an oversimplification, merely having someone on rounds each day to prompt the team to begin enteral feeding and to discourage irrational interruptions in support is valuable. Attention to immediate life-threatening concerns often lowers the perceived importance of problems that can affect the long-term quality of life. Perhaps no better example exists than lack of attention to physical therapy or occupational therapy needs. Saving the life of a young severe sepsis patient is profoundly rewarding until it is realized that the patient is left with lasting post-ICU syndrome or the potentially avoidable problems of footdrop and wrist contractures, which prevent return to employment and recreation. In addition, it has only recently been recognized that early mobilization of some critically ill patients accelerates ventilator weaning and ICU discharge. Therefore, it is important to involve physical and occupational therapists as soon as feasible during the ICU stay.

Table 19-1. Pharmacy Quality Improvement Strategies

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<tr>
<td>Elimination of unnecessary and duplicative medications</td>
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<tr>
<td>Dose adjustment optimization</td>
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<tr>
<td>Avoidance of drug interactions</td>
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<td>Substitution of less-toxic regimens of equal efficacy</td>
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<td>Substitution of less-costly regimens of equal efficacy</td>
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<td>Converting parenteral medications to an oral route as soon as feasible</td>
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<tr>
<td>Reducing the frequency of administration</td>
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<td>Avoiding drugs that require monitoring</td>
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<td>Preferential use of enteral nutrition</td>
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Outcomes, Processes, and Practices
Post-Intensive Care Syndrome

Since the beginning of critical care, there have been tremendous advances in the science and practices that allow more severely ill and injured patients to survive. However, negative long-term consequences for ICU survivors and families are a growing concern. ICU providers have always known that patients have a long road to recovery after transfer from the ICU. In the past two decades, however, research has revealed how remarkably common and devastating are the long-term consequences of critical illness. Although understanding is incomplete, these are almost certainly due in part to what we currently do to address disease and assure comfort.

Three emerging concepts are behind the recent emphasis on improving ICU outcomes. These include making safe transitions, emphasis on family-centered care, and acceptance that critical care is defined by the whole episode of care, not just the ICU stay. Post-ICU syndrome is defined as new or worsening impairment in physical, cognitive, or mental health status arising and persisting after hospitalization for critical illness. Physical consequences include weakness acquired in the ICU that occurs in a high proportion of patients receiving mechanical ventilation and treatment for sepsis. Many of these patients have weakness and/or mental impairment for months or years after the ICU stay. Such cognitive deficits include problems with memory, processing, planning, problem-solving, and visual-spatial awareness. Psychologic consequences include symptoms of depression, anxiety, sleep disturbance, and PTSD, which can last indefinitely. Many patients require caregiver assistance long after the precipitating ICU stay, and approximately 50% of previously employed patients who have had ARDS have not returned to work 1 year after discharge. Only a minority of patients receiving mechanical ventilation for more than 4 days are alive and independent 1 year later.

A number of strategies are being investigated to improve these results. Risk factors include number of days on mechanical ventilation, length of stay in the ICU, heavy sedation, delirium, sepsis, ARDS, hypoglycemia, and hypoxia. These aspects of ICU care should be the subject of quality improvement programs. Other specific strategies include limiting sedation and analgesia, promoting natural diurnal rhythms and sleep, exercise while bedridden, and early mobilization. Although resource intensive, the latter can be accomplished in those who continue on mechanical ventilation and even in the presence of invasive catheters or IV infusions. Many centers are beginning postdischarge follow-up programs to facilitate societal reintegration after the ICU stay. Early psychologic intervention may facilitate recovery of both patients and family members. One tool to aid the patient's mental processing of the ICU experience is creation of the ICU diary. This is a common practice in some European countries.

Many centers are beginning to apply the ABCDE bundle, which addresses the risks of sedation, delirium, and immobility. ABCDE stands for airway management, breathing trials, coordination of care and communication, delirium assessment, and early mobility. Additional proposed interventions include greater family involvement, follow-up referrals, and functional reconciliation with good handoff communication and handout materials to support understanding of the ICU stay.

Team Communication

An automobile journey would prove long, expensive, and potentially dangerous if there were no clear destination, defined route, and numerous people took turns driving. In the same way, successfully negotiating the path through the ICU becomes perilous and expensive if the “driver” does not understand the route or destination. It is also impossible to plan an efficient route without knowing all the relevant trip information. For most of the day, bedside nurses are the “drivers,” and if the plan and priorities are not clear, a wandering route is likely. For the ICU patient, confusion is manifest as redundant or irrelevant diagnostic testing, inappropriate therapeutic interventions, missed critical opportunities, and miscommunication.
The most practical solution to such problems is to have a senior physician lead the ICU team in executing a carefully developed plan. To accomplish this goal, it is essential to have at least daily multidisciplinary bedside rounds where participation (not just attendance) of key team members is required. This group should include the physician, nurse, pharmacist, dietician, and respiratory therapist. Attendance of consultant physicians is desirable but often not feasible. When circumstances suggest that they would be beneficial, occupational/physical therapists, social workers, case managers, palliative care specialists, and clergy should be included. Each day, the success or failure to achieve goals set the previous day should be evaluated. New problems and organ system function should be reviewed. Diagnostic information gained since the previous day and its implications should be discussed. The need for all medications, tubes, and catheters should be questioned. Changes in therapy should be agreed upon (not just what to do but in what order to do it, with contingency plans for unexpected events). The information to be communicated to the patient, family, and referring physicians should be discussed, and plans for transfer or discharge should be finalized. Following these steps all but guarantees that members of the team move efficiently in the same direction. This cooperative process offers the physician in charge the most current and accurate information upon which to make decisions, and as a major benefit, the staff becomes more cohesive, knowledgeable, happy, and respectful of one another.

In most hospitals, nursing and respiratory therapy personnel change shifts two or three times daily, whereas physicians typically transfer responsibilities less often. Personnel changes have advantages and disadvantages. Although a new caregiver provides a rested body and mind, the oncoming provider lacks key information and recent experience with the patient. The process of “handing off” a patient may occur much more frequently though than just once or twice daily as personnel may differ during transport of patients to or from the CT scanner, operating room, recovery room, or general care floor. It is important that transfers be done in an orderly and systematic way to prevent miscommunication. The oncoming staff must be made aware of the patient history, life support technology, medications, recent events and problems, and future plans. This review is often accomplished at two levels as bedside nurses exchange information and review medications, indwelling lines, and pertinent examination features. Separately, charge nurses review critical elements of illness and care to plan which nurses might need help or which patients are likely to require higher or lower levels of staffing. In the handoff process, respiratory therapists likewise review ventilator settings, treatment requirements, and recent problems and plans for weaning. For physicians, the process of care transfer often involves making formal bedside rounds together daily in teaching institutions. In nonteaching hospitals, a face-to-face or telephone exchange of information is often conducted.

Family Visitation and Communication

There is no blanket approach to family communication; rather, it is best to learn about the patient, family, and their preferences for receiving information and making decisions and then attempt to meet their goals. For example, do they want to attend rounds, have a face-to-face meeting daily, or talk by phone at a specified time? Including families in daily rounds is not an unreasonable option but can be time consuming and has met with mixed results. If done, it takes special physician talent to translate medical issues to lay language and answer questions accurately but efficiently while avoiding the appearance of haste. Some family desires cannot be met; no physician can meet or even call multiple family members at a set time each day. For especially large involved families, it is a very good idea to have them appoint a spokesperson with whom communication will occur if the entire clan is not in attendance. This practice obviously is not intended to withhold information from others who wish to be present for such discussions but rather to prevent physicians and nurses from being inundated by sometimes dozens of calls or visits each day requesting the same information. Furthermore, even when the exact same words are spoken to different family members, their interpretations are often dissimilar. As typically happens, after several family members compare what they “heard,” yet more calls are placed to the
doctor or nurse to reconcile seemingly discordant communications. Even when the message provided is consistent, the perception of the family is often one of inconsistency leading to dissatisfaction. It should be made clear to family that although most team members may have a good grasp of the current situation and progress, definitive information transfer and key decisions are best made through one identified caregiver, preferably the attending physician. In addition to scheduled discussions, families should be notified in a reasonable time frame of major changes in status including procedural complications, significant clinical deterioration or improvement, and certainly if the patient is being transferred from the unit. Because the time shortly after admission is particularly stressful, it is important not to let families languish without information during the period of initial evaluation and stabilization. Even a brief visit from the patient's nurse, the charge nurse, a doctor, or even a receptionist can be soothing. Keeping families updated on the progress of procedures and surgery is very comforting, especially if a procedure takes longer than planned or does not start when scheduled. Providing families a phone number that can be called at all times to obtain information should be a standard practice. It is important to respect confidentiality; hence, it is essential to find out if there are family members or friends who should not receive information—a practice that is facilitated by issuing passwords to persons authorized to receive information.

Clinicians must recognize the feelings of vulnerability experienced by family and patient in this life-threatening situation as well as the natural power gap perceived by the recipients of care and those who have responsibility for providing it. Trust between family and physician is nurtured by honesty and openness regarding diagnoses, expectations, and levels of doubt. Explaining the logic behind the management plan and the decision tree to be followed helps to reassure. Inquiry regarding the patient's occupation and vocational interests as well as the use of light and respectful humor whenever appropriate tend to forge the humanistic bonds needed to keep patient, family, and caregivers on the same side of the “fence.”

The policies surrounding visitation are highly variable, but more than two thirds of hospitals have some restrictions regarding the number of visitors and hours for visitation. Although some of these policies may simply be tradition, a sound case can be made for some periods of each day being visitor free (or limited). For example, space limitations in many ICUs practically limit the number of visitors at one time. Restricting visiting times can also be justified to guard the privacy of the patient being visited and other patients as they undergo physician examinations, bathing, and procedures. The presence of visitors can also hinder some important but routine duties such as handoffs, teaching rounds, and housekeeping functions.

Some family members have a driving need for physical proximity to the patient, wanting to stay at the hospital, sleep in the patient's room, and even help provide nursing care. Just as many family members care as deeply but cannot stand the sights, sounds, and smells of the ICU. For others, despite the strong desire to be present, their wishes cannot be fulfilled because of work or family obligations or simply geographic remoteness, and for them, a great guilt can result. Having families stay with patients for extended periods has good and bad aspects. Visitors can be very helpful in the care of patients or can be dangerous disruptions. Because of their familiarity with the patient, vigilant visitors can alert the staff to subtle findings that may presage a true physiologic crisis. A helpful visitor can also provide valuable information such as a patient's usual medications, allergies, and previous illnesses and therapeutic misadventures. In theory, visitors could even prevent problems like drug dosing errors, taking the wrong patient for a procedure, or performing an operation at the wrong site. Helpful visitors can offer the patient comfort and familiarity and sometimes can even be a care extender. When visitors participate in the care of the patient, valuable knowledge can be transferred that may be needed for a successful transition home (e.g., tracheostomy care), and they also get a realistic sense of how hard staff work and how many things must be done to care for a critically ill patient. Having a family member present can also enhance communication with other relatives who are not at the hospital.

On the other hand, a hypervigilant visitor can be a profound disruption if he or she obsesses over each beep or
buzzer resulting from a cough on the ventilator, the completion of a medication infusion, or a false heart rate alarm. Similarly, if visitors prevent patient rest, or cause frustration by repeatedly asking the same question of a patient with delirium or impaired communication, they can hinder good care. The continuous presence of visitors in the ICU can also present significant challenges to patient confidentiality and privacy. Special care should be taken to prevent visitors from overhearing conversations or seeing things relating to other patients that should remain confidential. Visitors also present important infection control issues, especially for patients in contact isolation because of transmissible infections. Visitors' failure to comply with isolation procedures can contaminate themselves and other visitors in the waiting area. Finally, the continuous presence of the same family member or visitor also presents a real problem of exhaustion and sleep deprivation for the visitor, because facilities for rest and nourishment are rarely adequate.

Critical illness is frightening, and each family member has a different desire for knowledge and a different way of coping with the stress. For some, acquisition of information is comforting. These family members relish participating in rounds, search the Internet, read informational pamphlets, ask probing questions about the diseases and procedures, and may even investigate the training and qualifications of the physicians and nurses. They often want to be present during procedures or sometimes even during cardiopulmonary resuscitation. Such family members appreciate the discussions of the risks and benefits of various possible courses of action. However, for just as many family members, the very same information is terrifying, incomprehensible, or overwhelming. For them, hearing about even minor and transient instability and trying to understand the meanings of laboratory and radiographic abnormalities are disconcerting. Similarly, team discussions of the likely next events or complications produce a sense of dread. All they really want to know are answers to simple questions like “Are the lungs getting better?” Family members also have vastly different responses to the inherent uncertainty of much of medicine, especially critical care. Learning that there may be disagreement about the best path to take or that some questions just cannot be answered can erode confidence in providers and sometimes even produces anger. “How could there not be an answer”?

Prognostication is difficult, yet it is one of the most desired features of family-physician communication. For some families, precision is important, insisting on specific “percentages,” but for others, questions are much more general: Do you think she will make it? Predicting outcomes is hard because except at the extremes of illness, survivability is uncertain. Because survival data are derived from populations and not individuals, it makes little sense to communicate prognosis with precision. No person has “55% mortality”—survival is dichotomous. For this reason, without being evasive, many clinicians use nonnumerical phrases like “hardly ever,” “very unlikely,” “more likely than not,” and “almost certainly” when describing outcomes. Another reasonable approach is to emphasize that outcome predictions come from populations using phrases like “Of 100 patients with a condition similar to your mother, 85 will survive.” The obvious problem is that there are not 100 patients sufficiently similar to anyone's mother to make such a comparison meaningful. Along similar lines, although approximations are often useful, it is often folly to provide families precise timelines for improvement, deterioration, or even death; doing so is doomed to failure. Projecting any precise time is probably going to be wrong, and when wrong, confidence in the providers is undermined not just for the patient at hand but also for future health care encounters. All experienced providers have heard something along the lines of “Five years ago the doctors told me my brother would not live through the night but lived almost a week,” usually implying but not saying “…so why should I believe you now?” Again the best course of action is to be as honest as possible in providing estimates of outcomes and timing while avoiding false precision.

It is important to explore cultural and religious issues with the family. In some cultures, life support is viewed as interference with the natural order; for others, not providing all available support is unethical. For some patients,
a successful outcome is defined as a well-functioning mind regardless of the state of the body; for others, physical limitations define failure. Some cultures find it incomprehensible that the patient is provided all the information regarding his or her condition, especially if the diagnosis is a terminal one like metastatic cancer. In other cultures, some diagnoses (e.g., severe sepsis) imply personal or moral failure and therefore are poorly accepted. For some patients, avoidance of transfusion and transplant is paramount, whereas others have specific prohibitions against use of recombinant or animal-derived medications. The only way to cope with the wide variety of beliefs and preferences is to talk openly with patients and families exploring these issues. A spiritual leader or clergyman of the patient's faith can be very useful to help the providers understand the patient's beliefs.

Families are particularly vulnerable to stress and anxiety during the time that the patient is in the ICU. Some family members develop symptoms that are not easily distinguished from PTSD. Quality communication that is perceived as empathetic decreases adverse psychologic outcomes in families of the critically ill. Making sure the family has frequent and understandable updates about patient condition and prognosis, incorporating family description of the patient's values and wishes into shared decision-making, and promoting family presence and participation in care are essential. Psychologists may facilitate family support and help them prepare for patient discharge. Families must be given help in developing the skills needed to care for the patient at home after discharge. Frequently, an ICU diary is helpful along with coaching of family members to take care of themselves.

Consent
Before performing nonemergent procedures or surgery, seeking informed consent from patients or assent from families is a common but far from uniform practice. Which risks are discussed and who carries out the discussion are highly variable. In addition, the procedures by which consent is sought vary by location with some hospitals seeking consent for transfusion, others for HIV testing, and some only for mechanical or surgical interventions. By contrast, formal consent or assent discussions using a detailed approved consent form are almost always required for the conduct of prospective human research. In both settings, the risks, benefits, and alternatives to the proposed intervention should be discussed and questions answered. It is best to think of consent as a process rather than an event where continuing discussions occur sometimes over hours or perhaps even days until the risks and benefits are clear. There is general agreement that consent is not required to perform immediately necessary lifesaving procedures (i.e., chest tube placement for tension pneumothorax). Despite the expectation to seek consent, there is a huge variability in the depth of information families seek during discussions, and little is known about what is actually understood. In fact, it is likely that no matter how well the discussion is conducted, there will be some knowledge deficit on the part of the patient or the family. In addition, there is legitimate debate about the value or need to seek reconsent for a third or fourth central line during a long ICU stay. Accordingly, some ICUs have adopted the approach of “preconsent,” whereby families are provided information regarding all commonly performed procedures at or near the time of admission and provide a single consent or assent for care. Although this practice makes sense in many ways, some practical issues can be envisioned. First, the sheer volume of information presented all at once might be overwhelming. Second, because the risks and benefits of any given procedure change somewhat over time, a discussion closer to the time of a given procedure might provide a more accurate assessment of the risk-benefit ratio. Moreover, a patient's or a family's acceptance of a given procedure may change over time as the patient improves or deteriorates, even if the risks and benefits have not changed. And finally, the legal validity of an all-encompassing consent remains open to debate.

Medical Errors and Adverse Events
Errors and complications occur in all phases of medical care, and it is unrealistic to think that all such events can
be avoided. It is important to have in place an effective program to try to continuously reduce errors and have a plan about what to do when errors are discovered. If errors are concealed only to be repeated, patients continue to be put at risk, and the system does not improve. Just as dangerous are accusatory investigational practices, which cultivate a culture of fear and cover-up. Clearly, patients and families should be made aware of errors as soon as they are known, and a reasonable amount of information can be provided regarding the cause and the effect on the patient. A good example would be informing the patient and/or family about a pneumothorax following central catheter insertion and laying out the plan to deal with the complication. In most cases, the potential for this adverse event should have already been discussed with the family or patient during the consent process—another reason for taking the consent process seriously. In other cases, it is clear that an error has occurred, perhaps administration of a medication to the wrong patient, but the reason for the error is not immediately apparent; here, inquiry is needed. Fortunately, in most such cases, there is no physical harm to the patient, but clearly even minor errors undermine the confidence in caregivers. An essential step to building quality is promoting a caregiving environment where factual error reporting is encouraged. For some employees to feel comfortable with the process, there must be a mechanism for anonymous reporting. The next step is an objective, dispassionate investigation to determine why the error occurred. Sometimes the cause is clear; in other cases, even extensive investigation cannot determine how an adverse event occurred. Some errors are so preventable that they should probably never happen: wrong patient or wrong-site surgery, for example.

Regardless, the goal should be zero errors, and whenever possible, systems should be put in place to prevent or minimize errors so that one does not have to rely on the flawless performance of individuals.

**Rapid Response, Transport, and Airway Teams**

For many patients transferring to the ICU from a general care floor, looking back on the 12 to 24 hours before admission is terrifyingly instructive, often like watching an accident occur in slow motion. Frequently, modest patient complaints and marginally abnormal vital signs are responded to in a leisurely series of escalating treatments, often ordered by telephone without physician examination. Occasionally, there are substantial delays between when physicians are called and when they respond. If there is an in-person examination, it is often conducted by a doctor unfamiliar with the patient. Commonly, the magnitude of physiologic abnormalities increases as does treatment intensity. Many times, nurses know the prescribed treatment is not working or the problem is more serious than the consideration it is being given. The most assertive and experienced nurses demand more aggressive action, but unseasoned or more timid nurses simply execute orders provided. The sense of the patient's downhill trajectory is often lost as personnel change shifts. Eventually, a crisis is manifested, and the patient suffers a cardiac or respiratory arrest or is rushed to the ICU in extremis. One way to lessen this all-too-common scenario is by developing independent in-house teams to respond to deteriorating patients that can be activated by anyone who perceives an impending crisis. These responders known variously as medical emergency teams (MET) or rapid response teams (RRT) now are extensively deployed. The composition of the responding teams varies widely but often includes an ICU charge nurse, a respiratory therapist, an advanced practice practitioner (where available), and a physician. The physician's background is highly variable, and he or she may be an emergency medicine doctor, an intensivist, a senior resident, or a hospitalist. Although many RRT activations end with transport of a critically ill patient to the ICU, many others do not; surprisingly, as many as 10% of MET/RRT calls end with a decision to not move the patient but rather establish comfort care with a “do not attempt resuscitation” designation. Another significant proportion of patients have a different or a more aggressive therapeutic approach initiated but are not moved to the ICU. In some cases, the call is merely a “false alarm.”

Some studies report dramatic (approx. 50%) reductions in unexpected cardiac arrest rates following
implementation of such teams, and for patients transferred to the ICU, shorter stays with better outcomes are the rule. In many cases, cost savings have been also demonstrated, probably because delaying transfer until a patient experiences a cardiopulmonary arrest on the floor is bad medicine and ends up costing more to treat multiple postarrest complications. Interestingly, in some studies, benefits of MET/RRT teams have not been observed. The reasons for such disparities are not certain; however, an explanation may stem from the pattern of use of such services. Amazingly, in many hospitals, well-trained, easily accessible MET/RRT groups exist, but they are called late or not at all. Reasons for suboptimal use might include inadequate staff education about the program, inability of the staff to recognize early signs of critical illness, established patterns of care, or fear of retaliation from the primary care team for usurping their authority. As a result, some hospitals are now experimenting with mandatory MET/RRT calls when patients reach certain physiologic or treatment thresholds.

**Admission and Discharge Practices**

To ensure that adequate resources are available to treat salvageable critically ill patients while costs are minimized, admission and discharge criteria must be implemented. These criteria should curtail the number of “unnecessary” admissions and minimize the safe length of stay. Admissions only for “observation,” in which no specific ICU intervention occurs, are probably most wasteful. Despite being at very low risk, patients who are admitted for observation still consume substantial resources and block access to the ICU for more seriously ill patients. This group, although fully deserving of close observation, should not occupy beds better used for those requiring intensive treatment. Furthermore, it is intuitive that such low-risk patients cannot experience an incremental benefit in outcome from ICU care because their prognosis is excellent to begin with. Stable postoperative patients and patients with diabetic ketoacidosis, hemodynamically stable gastrointestinal bleeding, and inconsequential drug ingestion constitute most of this group. The propriety of ICU admission for moribund patients or patients who choose not to receive life-support technology because of personal, family, or physician preference is also questionable. For such patients, palliative care or hospice services are much more appropriate; clearly, not all deaths must occur in an ICU. Research is now attempting to identify the patients likely to return to the ICU because they are liable to redevelop instability or are simply too much work for the staff of a regular hospital floor. Moreover, there obviously are times when patients not requiring the “technology” of the ICU are appropriately admitted for intensive nursing care or pain control.

**Triage**

There never seems to be enough beds in the ICU to meet peak demand, and a policy of “first come, first served” rarely provides an equitable solution for limited resources. Because each physician views (and should view) his or her own patient to be the most deserving of an ICU bed, someone must prioritize the need and adjudicate disputes. Thus, when the ICU is at 100% occupancy, it is important to have a triage officer to judge the severity of illness of both current ICU occupants and potential admissions. The triage function is best performed by an experienced critical care physician because although nurses usually have more than sufficient medical knowledge, they rarely have the political clout necessary to enforce a contentious decision. Triage problems are minimized when only a small number of trained critical care physicians admit patients to the ICU (a closed unit) and maximized when physicians with little ICU training or experience control the process. When triage is absent, the most powerful, persuasive, or persistent physician’s patient often is assigned the bed—not necessarily the patient who needs it most. In some hospitals, the emergency department physician determines the destination of each emergency admission, but obviously, this practice is flawed because that physician cannot know the condition of all other patients in the ICU. Furthermore, possibly the worst-case scenario occurs when a patient at another hospital is directly admitted “sight unseen” by any physician.
Prophylaxis Practices

Roughly a dozen practices are reasonably proven to be safe, cost-effective preventative therapies (Table 19-2). Because few people can reliably remember all these interventions, it makes sense to construct a “checklist” or standardized order set to prevent inadvertent omissions and to ensure appropriate application.

Treatment Protocols

Many physicians oppose the concept of using treatment protocols largely based upon three objections: (1) patients are too variable to have a set plan, (2) results of clinical trials do not translate to individual patients because of the study's inclusion and exclusion criteria, and (3) use of a plan or a protocol usurps the value of the expert clinician. Often, this debate is polarized with claims that treatment plans are always evil or good, but the truth certainly lies between these extreme positions. Protocols have immense value when the treatment plan is complex, especially if elements are time sensitive and there are steps that are likely to be overlooked or misapplied. Examples include initial evaluation of the trauma patient and early management of acute coronary syndrome, ischemic stroke, or septic shock. Protocols with a narrower focus are also helpful to empower nonphysicians to expedite the agreed-upon best practices (e.g., ventilator tapering, spontaneous breathing trials [SBTs], scale-targeted sedation, enteral feeding management). Even though it is hard for physicians to acknowledge the fact, many are not expert in all aspects of critical illness, and for them, having guidance on how to start treatment can be valuable. On the other hand, application of protocols to patients who should not receive them makes no sense and in some cases might be dangerous (e.g., permissive hypercapnia in the setting of intracranial hypertension). In addition, it is incumbent upon the physician ordering protocol-based treatment to know the exceptions to the protocol and when to reassess the plan. Deviation from protocol-based treatment is essential when the patient does not fit the protocol criteria or the plan fails. Regardless, if protocols are used, they should be carefully constructed and thoughtfully implemented. Whenever possible, performance data should be gathered to evaluate the success of such efforts.

Medical Records and Order Systems

Electronic medical records (EMR), order systems, and digital radiographs have improved care in many ways. Multiple persons can now simultaneously review the same record, even from remote locations. The “chart” or “films” are never lost, and changes to the medical record have clear date and time stamping. Legibility and clarity

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**Table 19-2. Prophylaxis Practices**

<table>
<thead>
<tr>
<th>Practice</th>
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<tbody>
<tr>
<td>Venous thromboembolism prevention</td>
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<tr>
<td>Gastrointestinal bleeding prophylaxis</td>
</tr>
<tr>
<td>Turning-repositioning decubitus ulcer prophylaxis</td>
</tr>
<tr>
<td>Pain control protocol</td>
</tr>
<tr>
<td>Targeted sedation protocol</td>
</tr>
<tr>
<td>Anemia prevention and transfusion protocol</td>
</tr>
<tr>
<td>Elevation of the head of the bed</td>
</tr>
<tr>
<td>Oral hygiene</td>
</tr>
<tr>
<td>Immunization—influenza, pneumococcal vaccine</td>
</tr>
<tr>
<td>Hand washing</td>
</tr>
<tr>
<td>Standardized enteral feeding protocol</td>
</tr>
<tr>
<td>Preprocedural “timeouts”</td>
</tr>
</tbody>
</table>

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of orders and notes are dramatically improved, and there is accountability if ordered treatments are not delivered in a timely fashion.

Apart from outpatient and inpatient histories, relevant published literature, hospital-generated policies and protocols, and educational materials are readily accessed from a single computer terminal. In addition, the ready availability of diagnostic test results and decision support tools, especially with regard to medication ordering, is a clear advantage of the electronic record. The EMR revolution has been quick, profound, and irreversible.

Unfortunately, however, electronic systems have produced some major problems. Remuneration often requires adequate and time-consuming documentation. Cutting and pasting is a tempting and often defensible time-saver but, apart from any questions of ethics, often replicates errors and outdated information. Some communications, especially those that require explanatory interaction, now occur electronically that are better conducted face to face. Among the worst problems result from nursing documentation systems, which use only standardized phrases or terms selected from a menu to document actions. Such charts are difficult to read and, in some cases, almost impossible to understand when the charting involves a string of digits that refer to standardized “footnotes.” Similarly, in an effort to standardize charting, the ability to enter free text descriptions is tacitly, if not overtly, discouraged. Sometimes, computerized nursing documentation is difficult to access and as a result less often read than in the past when the nurses’ notes were prominently displayed on a flow sheet at the bedside. In some electronic systems, the location of certain pieces of information is not intuitive, making it difficult for nonnurses to find them. As a result, understanding what really happened during a physiologic crisis becomes difficult if face-to-face communication with the nurse cannot occur. For physicians, there is a parallel problem. Instead of using handwritten-free text to describe the patient's problems and the thinking behind the decision-making, the physician's electronic note has devolved into little more than a list of “standardized diagnoses” for billing purposes. Both of these developments make it difficult to know what really happened to a patient, even when just a few days have passed.

Regrettably, care of the chart often takes priority over care of the patient as the near magnetic pull of the computer draws nurses and doctors away from the patient. This is especially problematic in hospitals where administrative electronic monitoring of documentation now occurs, putting unnecessary pressure on providers for “timely” documentation. Residents, too, face time pressure to complete documentation in an expedient fashion so as to finish all work before their mandated “off work”/hand-off deadlines. In such settings, nurses, respiratory therapists, and other personnel are placed on a treadmill where reaching documentation landmarks become a surrogate for effective care giving.

FACTORS INFLUENCING CRITICAL CARE COSTS

To many, “intensive care” equals “expensive care.” Unarguably, ICU care is costly; a patient's life savings can be spent quickly, with baseline costs in the United States now above several thousands of dollars per day. The approximately 10% of US hospital beds used for critical care generate nearly one third of all hospital charges; astonishingly, critical care expenses approach 1% to 2% of the US gross national product, with the vast majority of that money spent in the last few days or weeks of a patient's life. Even more impressive is that one clinical situation, the chronically ventilated patient, is responsible for half of all the money expended. With progressively more care being delivered in an outpatient setting, hospitals are devoting a higher proportion of beds to the critically ill.

Critical care is expensive for a variety of reasons, some influenced by patients and their families, some determined by physicians, and some as a result of the sheer volume, complexity, and cost of the treatments provided. An aging population brings many chronic problems to the hospital with each acute illness, making ICU admission ever more likely. It is not just the elderly patients who are incurring ICU costs, however; the increasing
frequency of trauma and prevalence of immunocompromise (e.g., HIV infection, transplants, and cancer therapy) account for the increasing demand for ICU care. Expanding numbers of middle-aged patients who suffer the effects of lifelong smoking, alcohol, inactivity, and obesity represent a large segment of the coronary care unit and medical ICU populations. Against the backdrop of increasing severity of illness and costs, the population has shown little restraint in its desire for critical care. The public perceives that miracles occur regularly in the ICU, and it seems that everyone wants his or her miracle when the need arises. This perception is not without some basis in fact: most large ICUs have mortality rates well under 20% despite a gravely ill patient group. In addition, in the last 10 years, dramatic progress has been made in severe sepsis and acute lung injury. Undoubtedly, a more realistic view of critical care by the public would help allocate limited resources most effectively, but there is little evidence that the public perception is changing. Likewise, physicians inexperienced in critical care frequently have unrealistic perceptions of the capabilities of the ICU.

Physicians and nurses also contribute to the high costs of critical care. Some of these costs are the result of well-intentioned desires to provide the best care; others are the result of inflexibility, intransigence, ignorance, and the practice of “defensive medicine.” Unfortunately, some members of the medical profession share the view, along with much of the rest of the society, that more is better. More diagnostic tests, more monitoring, more medicines, and longer stays all have been (consciously or unconsciously) equated with quality care. Furthermore, historically, physicians have been rewarded financially for increasing the resource use. Times are changing; we now recognize that more is often not better. For example, more blood sampling eventually causes anemia, requiring transfusion with its attendant risks and costs. “Unnecessary” tests will yield some false-positive results, which then prompt more, increasingly expensive, and potentially dangerous tests. More imaging studies expose patients to more radiation and radiographic contrast, often require travel from the ICU, and all such studies are expensive. Administration of radiographic contrast presents a special risk to patients with volume depletion, diabetes, or underlying renal insufficiency. More medications increase the risk of an adverse drug reaction often prompting additional diagnostic or therapeutic intervention. There are many examples, but in particular, imprudent use of antibiotics increases the risk of an antibiotic-resistant infection, not only for the treated patient but also for the subsequent patients admitted to the ICU.

Another factor leading to increased cost of care is physicians’ shortsightedness in not exploiting inexpensive or even free preventative measures to prevent catastrophic consequences. Examples include failure to use maximal barrier precautions when inserting vascular catheters, omission of deep venous thrombosis or gastrointestinal bleeding prophylaxis, and failure to elevate the head of the bed of mechanically ventilated patients. Finally, mortality, resource utilization, and costs may increase when physicians fail to adopt proven treatment strategies, such as lower tidal volume ventilation for acute lung injury.

Many practitioners have little idea what charges are attached to tests and treatments, and even when aware of costs, some believe that no amount is too much to spend, provided there is even a small chance of recovery. Although charges vary widely by region and hospital, Table 19-3 presents a realistic picture of the potentially staggering bill that can accrue on the first day in the ICU. Moreover, this illustration does not include charges for emergency services, surgery, transfusion, transportation, or physicians’ professional fees.

The ICU, like the emergency department, must be constantly prepared to accept a nearly unlimited number of admissions at any time and must be prepared to provide a full range of services for these admissions. Most US ICUs operate at approximately 85% capacity to satisfy this requirement for flexibility. In business terms, this excess capacity and its accompanying technology are “wasted.” Moreover, a perverse competition occurs as the hospital with the greatest range of services and amenities entices doctors to hospitalize patients in that facility, promoting geographic duplication of services. Regionalization of ICU care represents one potential solution to the problem
of excess capacity, but without strong financial incentives, it is not likely to occur.

Table 19-3. Itemized Typical ICU First-Day Charges

<table>
<thead>
<tr>
<th>Item</th>
<th>Charge (in $)</th>
</tr>
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<tbody>
<tr>
<td>Room</td>
<td>2,500</td>
</tr>
<tr>
<td>“Routine” admission laboratories</td>
<td>750</td>
</tr>
<tr>
<td>Blood, sputum, and urine cultures</td>
<td>250</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>100</td>
</tr>
<tr>
<td>Portable chest X-ray</td>
<td>150</td>
</tr>
<tr>
<td>Urinary drainage system</td>
<td>50</td>
</tr>
<tr>
<td>Mechanical ventilator</td>
<td>1,000</td>
</tr>
<tr>
<td>Noninvasive monitors (oximeter, blood pressure cuff)</td>
<td>100</td>
</tr>
<tr>
<td>Intravenous pump, tubing, and fluids</td>
<td>225</td>
</tr>
<tr>
<td>One intravenous antibiotic</td>
<td>150</td>
</tr>
<tr>
<td>Pulmonary artery monitoring catheter, tubing, and fluids</td>
<td>900</td>
</tr>
<tr>
<td>Simple sedative, analgesic regimen</td>
<td>200</td>
</tr>
<tr>
<td>Total</td>
<td>approx. 6,500</td>
</tr>
</tbody>
</table>

*a*Exclusive of physician fees.

Methods exist to reduce needless resource use and to eliminate waste. Unfortunately, rapid deployment of new operations, devices, and drugs, many of which have not been demonstrated to be sufficiently useful to justify their cost, inflate the price of care. It should be the role of the intensivist to ascertain the physiologic basis for deployment and to be certain that new technology passes muster for cost-effectiveness as well as safety and efficacy. To fully grasp the cost-control strategies, it is important to be able to distinguish costs from charges and to know the sources of ICU expenditures.

**DIFFERENCES BETWEEN COST AND CHARGE**

Charges are easy to measure. They are what patients and insurance companies are asked to pay and, at the hospital level, is the major determinant of the success or failure of attempting to secure contractual relationships
Patients are grouped for care because the cost of providing care for a specific diagnosis has multiple components, many of which, like utility or capital equipment costs, cannot be itemized but must be passed along to patients. Hence, arbitrary charges are set that vastly exceed true “cost.” Second, a large fraction of patients do not pay all or any of their bills, and these losses are recovered from private paying or insured patients. Third, some treatment options are so costly or used so rarely that no patient could bear the true cost. Therefore, charges are distributed, or “shifted,” to other patients who do not receive the service to ensure that the treatment remains available. For example, helicopter/air ambulance service is so expensive that users of the service cannot bear costs by themselves. This cost shifting is manifest as inflated charges for more commonly used therapies (e.g., “the $5 aspirin”). Moreover, certain high-volume services may be targeted as high revenue generators. Finally, over time, insurers and hospitals have come to agreement on “reasonable and customary charges” for services that do not even remotely reflect the cost.

Patient charges for a service, especially drug treatment, can differ greatly from the hospital’s acquisition cost for that drug because of the introduction of labor costs. For example, penicillin is a very inexpensive antibiotic to purchase; the cost for a day's supply of the intravenous form is probably less than $10. Why, then, is the daily patient charge likely to exceed $100? How could this drug be more expensive per day than an antibiotic costing 50 times as much per dose? The answers lie in the dosing schedule and costs for preparation. The less-expensive compound may require more frequent administration and laboratory monitoring. In the end, the patient is charged much more for this “less-expensive” drug because of the labor costs associated with repeatedly measuring, mixing, transporting, infusing, and monitoring the drug. The bottom line is that in today’s environment, costs do not equate with charges, and many hidden charges (e.g., drug toxicity and interactions and monitoring of levels) exist in prescribing a course of drug therapy; therefore, the cost of the entire therapeutic package must be considered.

**WHERE THE MONEY GOES**

Potential cost-control targets come from examining the pattern of ICU spending (Fig. 19-1). Well, more than half of expenditures go to labor costs (the largest portion of which is nursing salaries and benefits). About 10% to 15% of expenditures pay physicians; a similar amount is divided among other support personnel. It would be easy to say that fewer or less well-trained nurses (or physicians) are the answer, but generally you get what you pay for. Lower pay usually means less experience, and quality care is not delivered with fewer nurses or physicians or a less-qualified staff. In fact, perhaps the single most influential organizational factor for outcome is the nurse-to-patient staffing ratio. The use of physician assistants or nurse practitioners to provide critical care, especially after hours care, is in its infancy. It remains to be seen if outcomes will be better or worse and if sufficient numbers of practitioners can be trained and enticed into providing night and weekend coverage.
FIGURE 19-1. Typical distribution of intensive care unit spending. The majority (approx. 60%) of expenses are labor costs—in large part those necessary for constant bedside nursing. Costs for drugs, imaging procedures, laboratory studies, and supplies vary by individual patients, but each category averages about 10% of total expenses. This figure highlights the difficulty associated with significant cost reduction—substantial saving usually requires reducing personnel and risks lowering the quality of care.

As highly skilled and well-paid nurses are replaced with less-expensive “care extenders,” quality of certain essential ICU features may deteriorate. This process may have an unforeseen effect on professionalism, morale, and other difficult-to-quantify factors that reduce the efficacy and efficiency of care delivery. Furthermore, forcing highly trained health care professionals to undertake tasks for which they have little interest (e.g., supply restocking and cleaning), suboptimal training (e.g., phlebotomy), or inadequate experience (e.g., renal replacement therapy) is demoralizing and accelerates turnover. These problems can offset any potential cost saving, and over time, staff retraining becomes necessary. “Cross-training” ICU employees to perform a variety of tasks (e.g., food service, transport, phlebotomy, bathing, inventory, maintenance, and housekeeping) can reduce the total number of employees, but the reduction of lower-paying jobs results in little net cost savings. In addition, there can be adverse consequences. For example, shoddy phlebotomy technique resulting in contaminated blood cultures ends up being very costly. For the near future, major reductions in the single largest
area of expenditure, labor costs, seem unlikely.

Portions of ICU charges pass to the hospital to maintain the physical plant, durable equipment, required infrastructure (radiology, laboratory, etc.), and administrative staff and to provide a profit. The extensive administrative structure of managed care organizations and hospitals raises concerns that real cost savings will not happen; instead, funds will be redirected from patient care to administration. Although many methods of hospital-wide cost reductions are possible, they are well beyond the scope of this text.

RADICAL COST-CONTROL MEASURES

One way to reduce ICU costs is to limit resource availability. In many parts of the world, ICU beds constitute a tiny fraction of the total number of hospital beds—much smaller than in the United States. Limited availability means de facto “rationing,” a distasteful term for many. Undoubtedly, it would be reasonable to reduce or even eliminate ICU beds at many small hospitals in favor of transfer of critically ill patients to more specialized facilities, much like what is done with trauma victims or critically ill neonates. Doing so could eliminate the substantial capital and labor costs of having an ICU in the referring hospital and could improve the quality by getting sick patients to expert care. In addition, such a system could avoid any chance of biased referrals where tertiary care facilities are sent the critically ill uninsured patient but the insured patient remains at the original hospital. It is clear that patients who are transferred to tertiary facilities after a period of critical illness at a referring hospital have substantially worse outcomes and have more problems to care for.

Sadly, many existing cost-control measures have been arbitrary and externally imposed, rather than being thoughtfully, internally fashioned. Regardless of the source of the spending restraint, quality will suffer if cost becomes the major determinant of care. The most effective way to reduce overall hospital costs is to reduce the length of stay; the same is true for the ICU. The most obvious, radical, and possibly effective cost-control strategies (rationing admission, limiting the duration of support, or prohibition of certain therapies) are not now, and may never be, palatable to the public or to conservative physicians. Ideally, improved therapeutics shortens the ICU stay, resulting in a salutary effect on cost without such draconian measures. Dramatic therapeutic advances have occurred in sedation practice, glucose control, mechanical ventilation for acute lung injury, and treatment of severe sepsis. However, highly effective cost-control strategies also include those that affect logistics and process of care delivery: making optimal use of available beds, minimizing labor costs, improving efficiency of care delivery, and reducing equipment, imaging, laboratory, and drug expenditures.

SPECIFIC COST-CONTROL SUGGESTIONS

Imaging Costs

Imaging studies account for 10% to 20% of an ICU patient's hospital charges. In addition, use of radiographic contrast media can cause catastrophic and expensive complications (e.g., acute kidney injury). Furthermore, many of today's imaging studies require costly transport to the radiology department, during which time any number of complications can occur. Thus, reducing the number of radiological studies can trim costs in at least three ways. Strategies to sensibly limit the procedures include (1) eliminating low-yield portable studies (e.g., supine abdominal film, sinus studies, bone films); (2) for stable patients, reducing the frequency of “routine” studies, especially the daily portable chest X-ray (CXR); (3) when two options of comparable quality and cost exist, using the one that can be performed in the ICU to avoid transport costs and risks; (4) optimizing scheduling to minimize the number of trips to the radiology department; (5) using the absolutely necessary visits to the radiology department as an opportunity to substitute higher-quality images for less-optimal portable studies; (6) when a series of procedures are done in rapid succession, wait until all are completed to obtain the single
radiograph needed to evaluate results, device placement, and complications; (7) putting in place measures to avoid or minimize radiographic contrast exposure, especially in patients at highest risk for injury; and (8) when a diagnostic study is performed in the radiology department, it should be interpreted immediately so that additional views, complementary studies, or therapeutic intervention can be performed without a second trip. (This mandates the ready availability of a physician decision-maker.)

Even though some studies are ordered by custom, they are of low yield or only partially informative. One example is the supine abdominal film—even though it may rarely find free air or intra-abdominal calcifications, sensitivity is very low, and even if positive, almost certainly a more detailed study will be required before definitive intervention. For this reason, if viscus perforation or obstructive uropathy is suspected, it probably makes most sense to proceed directly to an abdominal CT scan or ultrasound, respectively.

Overall, the portable CXR is the most common and costly radiographic procedure for most ICU patients. As discussed in Chapter 11, the CXR provides vital information but has many limitations. Unless imaging guidelines are established, some ICU patients undergo one to two portable CXRs each day, often without strong indication. The practice of ordering routine daily CXRs should be reconsidered. Forgoing routine daily CXRs for stable patients (even those on mechanical ventilators) is safe and can reduce imaging costs by up to one third. Obviously, a clinically significant change in cardiopulmonary status should prompt consideration of a CXR, as should insertion or manipulation of tubes or catheters. Practically, even when routine films are not obtained, patients may have one CXR each day because of changing physiology or insertion of monitoring devices. Additional savings can be had by performing only one CXR after a series of procedures (e.g., thoracentesis, intubation, central catheter insertion) instead of a film between each intervention. Obviously, imaging should not be delayed if a life-threatening complication from any procedure is suspected.

Other potential cost savings can be realized when patients must leave the ICU for an imaging study. Substantial expense and risk are associated with transporting patients from the ICU—one report suggests costs of several hundred dollars for transport alone. Regardless of the true cost, it makes sense to travel as little as necessary. When a diagnostic study can be performed in the ICU with comparable quality to that performed in the radiology department, opting for the portable examination avoids transport cost, discomfort, risk, and inconvenience. One example would be the search for gallstones or biliary obstruction, in which both portable ultrasound and department-based CT scan are viable options, but the portable study offers substantial cost advantage. Another example of when ICU imaging could avert a trip to the radiology department is with regard to thromboembolism diagnosis. A patient with a suspected pulmonary embolism could have the diagnosis of venous thrombosis confirmed by portable ultrasound of the legs instead of traveling for a chest CT. In the vast majority of cases, the treatment will be identical for the diagnosis of deep venous thrombosis and pulmonary embolism, and such a strategy avoids contrast and ionizing radiation exposure.

Arranging several studies to be performed in the radiology department during the same visit is also cost-effective. For example, if plans exist to perform an elective chest CT today and head CT tomorrow, it is reasonable to consider rescheduling to accomplish both in a single trip. Finally, it makes sense to anticipate the need for therapeutic intervention when ordering diagnostic studies. For example, a patient with pancreatitis experiencing high fever and clinical deterioration is likely to have an area of the pancreatic bed that will need to be aspirated or drained. Thus, it makes great sense to plan the aspiration at the time of initial imaging and then abort the intervention if not necessary.

**Supplies**

Equipment savings can be substantial if stocking is well planned. Almost all disposable equipment (e.g., sutures, dressings, sterile trays, intravenous and suction catheters) has an expiration date. None of these items are
inexpensive, and careful inventory will often reveal that much is discarded because it “expired” without ever being used. The justification for continued stocking of seldom-used items is often “we needed it once.” It makes sense not to do away with immediately essential equipment but to reconsider all materials stocked. Limit the variety and quantity of supplies to a safe level that minimizes waste. For example, many different sizes and types of tracheal suction catheters or pulmonary artery monitoring catheters are not necessary. Likewise, it is not necessary to have immediately available every type and size of suture and needle. Determine what is used regularly and what is rarely used but must be available immediately. Stock only those items, and stock them in reasonable quantities.

A considerable amount of time can be saved and complications avoided if sets of commonly used supplies are packaged together. One example is placing all needed materials for central venous catheter insertion in a single container. Packaging in this way not only saves time but also encourages best insertion practice by ensuring that the appropriate disinfectant, gowns, gloves, caps, drapes, etc. are all present.

**Respiratory Therapy**

A simple, effective, cost-control measure involves the process of discontinuing invasive ventilator support. For most patients, “weaning” is neither complex nor prolonged. Because many physicians do not consider withdrawal of mechanical ventilation until certain targets are met for FiO\(_2\) and positive end-expiratory pressure (PEEP), it makes sense to empower the respiratory therapist to automatically reduce the levels of support using predetermined unit-based guidelines. Doing so can reduce the time required for a patient to “qualify” for a SBT. The vast majority of patients who are not in shock and who receive ≤10 cm H\(_2\)O of PEEP and an FiO\(_2\) ≤ 0.5 can safely undergo an SBT conducted by nurses or respiratory therapists using an established protocol. When spontaneous breathing is tolerated for 30 to 120 minutes (under observation), the physician can be consulted for a decision to extubate. Making the process of testing automatic avoids inherent delays in physicians “ordering” an SBT or, even worse, overlooking the possibility altogether.

Other simple measures can safely decrease costs of the weaning process. One is to avoid “T-piece” weaning. Charges for the equipment and labor for setup are often substantial; instead, use the continuous positive airway pressure (CPAP) mode of the ventilator. When necessary, CPAP can be combined with a low level of pressure support to overcome intrinsic resistance of the ventilator circuit. For most patients, no significant increase in work of ventilation is realized in breathing through well-adjusted ventilator circuitry, and the machine provides the advantage of an “apnea alarm.” Another example is to immediately place most patients on nasal cannula oxygen rather than some variety of mask or face tent after extubation. In common practice, the mask is discarded within minutes or hours in favor of a nasal cannula anyway. Going directly to the cannula avoids the cost of the equipment and therapist time. Obviously, patients extubated from high FiO\(_2\) and those with conditions that would impede nasal oxygen flow are poor candidates for such a strategy. For some tenuous patients, however, high-flow nasal cannula systems offer significant potential advantages over conventional masks in comfortably assisting oxygenation and CO\(_2\) exchange. Finally, once the patient is extubated, remove the ventilator from the room if safe to do so. When not connected to the patient, the ventilator offers little more than expensive psychological comfort. Many hospitals charge ventilator fees in 12-hour blocks, and if the ventilator is still in the room, the patient will be charged for unneeded equipment.

In many cases, additional savings can be realized through the use of metered-dose inhalers (MDIs) instead of updraft nebulizers, which require more time to deliver and more therapist time. For most spontaneously breathing patients, MDIs are capable of providing similar bronchodilating effect provided that multiple device actuations are administered. Use of MDIs is particularly advantageous for the intubated patient because the bias flow of an in-line nebulizer can create triggering problems and obscures the evaluation of minute ventilation.
Dramatic charge reductions can also be realized by substitution of long-acting inhaled drugs for short-acting medications. For example, hundreds of dollars a day in charges can be avoided by using once-daily tiotropium and patient-administered short-acting beta agonist compared to repeated nebulized doses of an ipratropium-albuterol product. Finally, the common practice of routinely providing most or all mechanically ventilated patients with inhaled bronchodilators should be reconsidered. Obviously if bronchospasm is present on exam, such treatment makes sense, but the mere use of mechanical support does not justify universal application of bronchodilator therapy.

**LABORATORY STUDIES**

Legitimate concern over physiologic and chemical abnormalities is a major factor driving laboratory use. Unfortunately, the range and frequency of laboratory use are determined in large part by habit and physician comfort and experience in the care of critically ill patients. For example, less-experienced physicians often order chemistry and hematology profiles and blood gases daily. In addition, standing orders for blood, sputum, and urine cultures are often written to evaluate temperature elevations. Frankly, there is little justification for such rigid practices; more flexibility and thought are often required. Although laboratory use should be customized for each patient, reasonable guidelines for the frequency of laboratory monitoring for the “average” patient can be proposed (Table 19-4). In addition, there are numerous studies demonstrating that development of testing guidelines decreases laboratory use without compromising outcomes.

Another underappreciated problem is that of improper sampling. In some hospitals, up to 25% of samples delivered to the clinical laboratory are improperly collected or labeled. The majority of these “preanalytical” errors are underfilled tubes, blood collected in the wrong tube, or mislabeled or inadequately labeled samples. In many cases, this results in the sample being discarded. The impact in terms of wasted time and blood is enormous, and it logically follows that at some point, wasted blood will be replaced by transfusion. The problem of mislabeled samples is particularly keen if the sample is unique or difficult to obtain (e.g., spinal or bronchoalveolar lavage fluid). Clearly, measures such as point-of-care testing and dedicated phlebotomy teams should be implemented to prevent this wasteful practice.

**Microbiology Laboratory**

Fever evaluations are most fruitful when performed for new-onset fever in the absence of antibiotic therapy. A temperature threshold for obtaining cultures of less than 96°F or more than 101.4°F is rational in the absence of other alarming indicators. For patients with continuous or near continuous fever, it is reasonable to repeat cultures every 3 days, an interval sufficient for full evaluation of previously obtained cultures and for empiric antibiotics to work. An obvious exception includes patients with suspected endocarditis or septic thrombophlebitis in whom bacteremia may be continuous and patients who have dramatic physiologic deteriorations associated with worsening of fever. Up to one half of all “positive” blood cultures grow organisms ultimately deemed to be “contaminants.” These false-positive cultures incite costly intervention, as they prompt additional diagnostic studies (more cultures and imaging studies) and antibiotic therapy and may prolong hospital stay. Meticulous technique for obtaining blood cultures, perhaps even using trained phlebotomists, will minimize the problem of contamination.

**Table 19-4. One Scheme for ICU Laboratory Monitoring**

| All Patients on Admission |
12-lead electrocardiogram
Portable chest radiograph
Urinalysis
Hemoglobin, platelet count, and white cell count with differential
Automated chemistry profile
Electrolytes Na\(^+\), K\(^+\), Cl\(^-\), \(\text{HCO}_3^-\)

Liver function tests: serum aspartate amino transferase, serum alanine amino transferase, bilirubin, alkaline phosphatase
Renal function tests: creatinine, blood urea nitrogen
Nutritional indices: cholesterol, total protein, albumin
Glucose
Prothrombin time

Individualized Studies

Arterial blood gas
Partial thromboplastin time
Magnesium
Calcium
Creatinine phosphokinase
Brain natriuretic peptide
Troponin
Blood, urine, sputum cultures

Daily Assessment for Patients with Hemodynamic or Respiratory Instability

Respiratory Instability
Portable chest radiograph
Electrolytes
Creatinine, blood urea nitrogen
Glucose
White blood cell count, hemoglobin

After Stabilization (tests to be done once or twice weekly)

Electrolytes and renal function tests
Hemoglobin, platelet count
Portable chest radiograph
Automated profile of nutritional status and liver function
Arterial blood gas

Indications for Cultures

New-onset fever or hypothermia
Reculture approximately every 3 days for persistently febrile patients
New, unexplained hemodynamic or respiratory deterioration
**Chemistry Laboratory**

Evaluation of electrolytes is often prudent several times a day during a period of instability, especially early in the hospitalization. During this time, provision or removal of large amounts of fluid often leads to important changes in sodium, chloride, and potassium concentrations. Likewise, acid-base disorders alter the bicarbonate and potassium levels in these unstable patients. However, after 2 to 3 days in the ICU, daily chemistry evaluations are needed in relatively few patients. Granted, patients with acute renal failure, especially those receiving renal replacement therapy, and patients with severe hypokalemia or hyperkalemia warrant more frequent monitoring. Although very reasonable on admission, detailed automated blood chemistry profiles are rarely needed more than once weekly. If specific components of the profile are necessary (e.g., liver function tests, albumin), it is often more cost-effective to order the individual components. When automated chemistry profiles are used to track nutritional status, evaluation at more than weekly intervals is probably wasteful; the slow pace at which nutritional parameters change makes more frequent monitoring imprudent.

It is also wasteful to repeatedly monitor the values without instituting reasonable corrective action. A good example is potassium replacement in patients with severe hypokalemia. When potassium values fall below 3 mEq/dL, administering 20 or 40 mEq of potassium and rechecking the value are near useless—the ion deficit is usually close to ten times as great.

Perhaps two of the most overused chemistry tests are those for calcium and magnesium. As largely intracellular cations, both are highly susceptible to variations in plasma protein concentration and acid-base status changes. In addition, changes in plasma values have little biological effect over broad ranges. Unless obtained to evaluate a specific clinical problem (e.g., refractory arrhythmia, neuromuscular weakness, or irritability), neither test is likely to be helpful. Because the therapeutic margin of magnesium is broad unless the patient has significant renal insufficiency, a very reasonable strategy is to simply administer magnesium in situations where depletion is likely and potentially related to clinical findings. Magnesium depletion is common in the same clinical situations in which hypokalemia is observed (diuretic use, alcoholism, etc.) (Table 19-4).

**Hematology Laboratory**

Like chemistry measurements, with some notable exceptions, daily or more frequent monitoring of hemoglobin, platelet count, and white blood cell count is probably not necessary after the initial period of instability. Patients undergoing therapeutic anticoagulation are prone to declines in hematocrit and possibly the thrombocytopenic effects of heparin suggesting that monitoring should be more frequent. Thus, once-daily monitoring of each parameter is not unreasonable. Similarly, patients with active hemorrhage (especially trauma victims, patients with active gastrointestinal bleeding, and others receiving transfusion) probably should be monitored on at least a daily basis. But even for these patients, there is potential for cost reduction: white blood cell, particularly differential, counts are not necessary for patients in whom the purpose is to track hemorrhage. Furthermore, differential counts are seldom helpful after admission, except for patients with neutropenia from sepsis or chemotherapy.

**Coagulation Laboratory**

Tests of coagulation frequently are abused at great expense. At the time of admission, it is very reasonable to assay the prothrombin time (PT). Measuring the activated partial thromboplastin time (aPTT) is unlikely to yield useful information unless heparin therapy or hereditary coagulopathy (e.g., hemophilia, von Willebrand's) is suspected. The combination of normal PT and aPTT all but excludes hereditary coagulopathy, consumptive coagulopathy, and profound nutritional deficiency. After admission, the PT is subject to change by consumption,
dilution, or decreased production of vitamin K-dependent clotting factors. Hence, disseminated intravascular coagulation (DIC), dilutional coagulopathy, progressive liver disease, or warfarin anticoagulation would be a clear indication for monitoring the PT over time. The PT will not respond quickly to warfarin therapy and is essentially useless as a measure of heparin effect. The aPTT is increased by dilution, consumption, heparin therapy, or congenital coagulopathy. Therefore, it is reasonable to obtain aPTT measurements for patients being treated for DIC or dilutional coagulopathy, and it is essential for patients being treated with continuous infusion unfractionated heparin therapy. There is no indication for repeated aPTT determinations in patients being treated with low molecular weight heparin or those receiving warfarin alone.

Another coagulation test that is vastly overused in the hospitalized patient population is the D-dimer test. Although a low result from an ultrasensitive D-dimer test is very useful in the outpatient setting to truncate the evaluation of venous thromboembolism, testing is usually wasteful among inpatients. Essentially every condition, which provokes ICU admission (e.g., surgery, trauma, severe sepsis, hepatic failure, DIC, etc.), also raises the D-dimer, negating its usefulness for exclusion of thromboembolism.

Blood Gases
Before wide application of pulse oximetry and realization that the arterial CO$_2$ concentration rarely needs to be normalized, arterial blood gases (ABGs) were recommended after every ventilator change and were performed routinely on a daily basis for ventilated patients. Even daily ABGs are not necessary in the absence of a change in clinical status or noteworthy ventilator parameter change. Furthermore, changes in administered oxygen concentrations do not routinely require ABGs when saturation is monitored. In several centers, the application of simple clinical guidelines as to when ABGs should be obtained has been associated with dramatic declines in use without detectable harm. Obviously, ABGs prove most useful in the initial period of hemodynamic and ventilatory instability or when metabolic acid-base disorders are suspected (see Chapter 5). There have been numerous advances in capnography technology, but it still has limited value among patients with advanced lung disease in whom end-tidal CO$_2$ rarely equilibrates with arterial CO$_2$. Despite its limitations, capnography is useful for confirmation of proper endotracheal tube placement and as an early warning to airway loss during the transport of patients. When clinically indicated, ABGs are still necessary for evaluation of arterial CO$_2$ content in patients with severe lung disease.

SUMMARY
Dedicated and experienced leadership; a team approach to care; defined procedures for admission, discharge, and transfer; restriction of attending privileges; and comprehensive guidelines for the use of drugs, imaging studies, and laboratory tests can produce substantial cost savings while simultaneously improving the quality of care. Clear, frequent, and face-to-face communications among health care providers and with patients and families are essential for good outcomes. In the end, the best hope for cost containment and quality care lies in the education of caring physicians and nurses, so they can choose wisely from the ever-expanding set of diagnostic and therapeutic alternatives.

SUGGESTED READINGS


Chapter 20
Cardiopulmonary Arrest

• Key Points

1. The success (hospital discharge without neurological impairment) of cardiopulmonary resuscitation is highly variable among patient populations. Cardiopulmonary resuscitation is very effective when applied promptly to patients with sudden cardiac death because of electrical instability, but is quite ineffective when applied in chronically debilitated patients and those suffering arrest as part of the natural progression of multiple organ failure.

2. The goal of resuscitation is to preserve neurological function by rapidly restoring oxygenation, ventilation, and circulation to patients with arrested circulation.

3. The resuscitation status of every patient admitted to the ICU should be considered at admission. When a clear determination regarding resuscitation status cannot be made quickly, the physician generally should err on the side of promptly initiating resuscitation efforts. Obvious exceptions to this recommendation apply when cardiopulmonary resuscitation is prohibited by patient mandate or not indicated because it cannot produce successful results.

4. Most successful resuscitations require only 2 to 3 minutes. In these, establishing a patent airway and promptly applying direct current shocks to reestablish a perfusing rhythm are the key actions necessary. It is quite uncommon to successfully resuscitate a patient after more than 20 to 30 minutes of effort. A notable exception to this rule occurs in patients with hypothermia who are occasionally resuscitated after hours of effort.

5. Although widely published guidelines provide a framework for resuscitation, cardiopulmonary arrest in a hospitalized patient often has a specific cause; therefore, resuscitative efforts should be individualized. Common situations are outlined in Table 20-1.

6. In most cases, reestablishing an effective rhythm involves either the application of direct current shocks to terminate ventricular fibrillation or tachyarrhythmia or the acceleration of bradyarrhythmias.

7. Although the systemic acidosis seen in patients with circulatory arrest can be buffered with NaHCO₃, a better strategy is to optimize ventilation and circulation. NaHCO₃ should not be used routinely but retains a role for specific arrest circumstances such as tricyclic antidepressant overdose, hyperkalemia, and extreme acidosis.

By necessity, most recommendations for treating cardiopulmonary arrest are not derived from high-quality randomized human studies but rather from retrospective series, animal experiments, and expert opinion. Treatment recommendations traditionally have been most applicable to patients who sustained sudden cardiac catastrophes, especially those occurring outside the hospital. Because the focus of this book is on the hospitalized critically ill patient, some of the discussion that follows will naturally differ from widely disseminated recommendations. Most arrests among patients with ischemic heart disease are due to ventricular tachycardia (VT) and ventricular fibrillation (VF). As a corollary, because pulseless VT or VF is so likely to be the cause of death in the cardiac ICU, such patients should almost always be treated immediately with unsynchronized cardioversion. By contrast, a respiratory event (aspiration, excessive sedation, pulmonary embolism,
airway obstruction) is much more likely to occur at other sites in the hospital. It follows that arrests on a hospital ward or noncardiac ICU are more likely to respond to a directed intervention beyond a cardiac rhythm change, often one involving the lungs.

### Table 20-1. Common Clinical Scenarios of Cardiopulmonary Arrest

<table>
<thead>
<tr>
<th>Setting</th>
<th>Likely Etiology</th>
<th>Appropriate Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>During mechanical ventilation</td>
<td>Misplaced ET tube, Tension pneumothorax, Hypovolemia, Auto-PEEP, Hypoxemia, Mucus plugging</td>
<td>Confirm proper location by visualization and auscultation, CO₂ detector, Physical examination, chest tube placement, Fluid bolus, Reduce minute ventilation, increase expiratory time, bronchodilator, suction airway, Check ET tube placement, oximeter saturation; administer 100% O₂, Suction airway</td>
</tr>
<tr>
<td>Postcentral line placement/attempt</td>
<td>Tension pneumothorax, Tachyarrhythmia, Bradycardia/heart block</td>
<td>Physical examination, chest tube placement, Withdraw intracardiac wires or catheters; consider cardioversion/antiarrhythmic, Withdraw intracardiac wires or catheters, consider chronotropic drugs, temporary pacing</td>
</tr>
<tr>
<td>During dialysis or plasmapheresis</td>
<td>Hypovolemia, Transfusion reaction, IgA deficiency: allergic reaction, Hyperkalemia</td>
<td>Fluid therapy, Stop transfusion; treat anaphylaxis, Stop transfusion; treat anaphylaxis, Check K⁺; treat empirically if ECG suggests hyperkalemia</td>
</tr>
<tr>
<td>During transport</td>
<td>Displaced ET tube, Interruption of vasoactive drugs</td>
<td>Early identification using end-tidal CO₂, Restart IV access</td>
</tr>
<tr>
<td>Acute head injury</td>
<td>Increased intracranial pressure (especially with bradycardia), Diabetes insipidus: hypovolemia (especially with tachycardia)</td>
<td>Lower intracranial pressure (ICP): hyperventilation, mannitol, 3% NaCl, Administer fluid</td>
</tr>
<tr>
<td>After starting a new medicine</td>
<td>Anaphylaxis (antibiotics)</td>
<td>Stop drug; administer fluid, epinephrine, corticosteroids</td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------------------------</td>
<td>--------------------------------------------------------</td>
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<tr>
<td></td>
<td>Angioedema (ACE inhibitors)</td>
<td>Volume expansion</td>
</tr>
<tr>
<td></td>
<td>Hypotension/volume depletion (ACE inhibitors)</td>
<td>Methylene blue</td>
</tr>
<tr>
<td></td>
<td>Methemoglobinemia</td>
<td></td>
</tr>
<tr>
<td>Toxin/drug overdose cyclic antidepressants β-blocker/Ca²⁺ blocker</td>
<td>Seizures/tachyarrhythmias</td>
<td>Sodium bicarbonate</td>
</tr>
<tr>
<td></td>
<td>Severe bradycardia</td>
<td>Chronotropes, pacing, glucagon, insulin + glucose</td>
</tr>
<tr>
<td></td>
<td>Severe bradycardia</td>
<td>Decontamination, atropine, pralidoxime</td>
</tr>
<tr>
<td>Organophosphates</td>
<td></td>
<td></td>
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<tr>
<td>Carbamates</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>After myocardial infarction</th>
<th>Tachyarrhythmia/VF</th>
<th>DC countershock, lidocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Torsades de pointes</em></td>
<td></td>
<td>Cardioversion, Mg, pacing, isoproterenol, stop potential drug causes</td>
</tr>
<tr>
<td>Tamponade, cardiac rupture</td>
<td></td>
<td>Pericardiocentesis, fluid, surgical repair</td>
</tr>
<tr>
<td>Bradycardia, AV block</td>
<td></td>
<td>Chronotropic drugs, temporary pacing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>After trauma</th>
<th>Exsanguination</th>
<th>Fluid/blood administration, consider laparotomy-thoracotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tension pneumothorax</td>
<td>Physical examination, chest tube placement</td>
</tr>
<tr>
<td>Tamponade</td>
<td></td>
<td>Pericardiocentesis/thoracotomy</td>
</tr>
<tr>
<td>Abdominal compartment syndrome</td>
<td></td>
<td>Measure bladder pressure; decompress abdomen</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Burns</th>
<th>Airway obstruction</th>
<th>Intubate</th>
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<tbody>
<tr>
<td></td>
<td>Hypovolemia</td>
<td>Fluid administration</td>
</tr>
<tr>
<td></td>
<td>Carbon monoxide</td>
<td>100% O₂</td>
</tr>
<tr>
<td></td>
<td>Cyanide</td>
<td>Hydroxocobalamin</td>
</tr>
</tbody>
</table>

ABG, arterial blood gases; ACE, angiotensin-converting enzyme; AV, atrioventricular; DC, direct current; ECG, electrocardiogram; ET, endotracheal; PEEP, positive end-expiratory pressure; VF, ventricular fibrillation.

**PRIMARY PULMONARY EVENTS (RESPIRATORY ARREST AND SECONDARY CARDIAC ARREST)**

Patients found unresponsive without respirations but with an effective pulse have suffered a respiratory arrest. Failure to rapidly restore ventilation results in hypoxemia and progressive acidosis that culminates in reduced contractility, hypotension, and eventual circulatory collapse. Although the etiology of many respiratory arrests remains uncertain even after thorough investigation, the cause often can be traced to respiratory center depression (e.g., sedation, coma, stroke, high intracranial pressure) or to failure of the respiratory muscle pump (e.g., excessive workload, impaired mechanical efficiency, small or large airway obstruction, or muscle weakness). Tachypnea usually is the first response to stress, but as the burden becomes overwhelming, the
respiratory rhythm disorganizes, slows, and eventually ceases. Initially, mild hypoxemia enhances the peripheral chemical drive to breathe and stimulates heart rate. Profound hypoxemia, however, depresses neural function and produces bradycardia refractory to autonomic influence. At this point, cardiovascular function usually is severely disordered, both because cardiac and vascular smooth muscle function poorly under conditions of hypoxia and acidosis and because cardiac output falls as heart rate declines. The observation that nearly one half of hospitalized cardiopulmonary arrest victims exhibit an initial bradycardic rhythm underscores the role of respiratory causes of circulatory arrest.

FIGURE 20-1. Change in arterial partial pressure of oxygen and carbon dioxide after respiratory arrest (normal lungs). Oxygen concentration falls precipitously to dangerously low levels within minutes. By contrast, the rise in carbon dioxide tension is much slower, requiring 15 to 20 minutes to reach levels sufficient to produce life-threatening acidosis.

In many critically ill patients, the arterial partial pressure of oxygen (PaO₂) plummets shortly after ventilation ceases because limited O₂ stores are rapidly consumed. Reserves are diminished by diseases that reduce baseline saturation (e.g., chronic obstructive pulmonary disease [COPD], pulmonary embolism), lower functional residual capacity (e.g., morbid obesity, pregnancy), or both (e.g., pneumonia, pulmonary fibrosis, congestive heart failure). Ambulatory patients who suffer sudden cardiac arrest usually draw upon substantially greater O₂ reserves because they typically do not have diseases causing significant desaturation or thoracic restriction at baseline. For this reason, attention to oxygenation is much more important in the hospitalized respiratory arrest victim, whereas establishing artificial circulation and prompt rhythm correction are priorities for the “cardiac” death patient. Unlike O₂, CO₂ has a huge storage pool and an efficient buffering system. Therefore, PaCO₂ initially builds rather slowly, at a rate of 6 to 9 mm Hg in the first apneic minute and 3 to 6 mm Hg/min thereafter (Fig. 20-1). However, as the apneic patient develops metabolic acidosis from tissue hypoxia, H⁺ combines with
to dramatically increase the rate of CO₂ production. The net effect of these events is that life-threatening hypoxemia occurs long before respiratory acidosis itself presents a major problem.

**PRIMARY CARDIOVASCULAR EVENTS (CARDIOPULMONARY ARREST)**

The heart may abruptly fail to produce an effective output because of arrhythmia or suddenly impaired pump function resulting from diminished preload, excessive afterload, or decreased contractility. The normal heart compensates for changes in heart rate over a wide range through the Starling mechanism. Thus, cardiac output usually is maintained by compensatory chamber dilation and increased stroke volume despite significant slowing of rate. Children and adults with dilated or noncompliant hearts have less reserve and are highly sensitive to bradycardia.

Decreases in left ventricular preload sufficient to cause cardiovascular collapse usually are the result of venodilation, hemorrhage, pericardial tamponade, or tension pneumothorax. In contrast to the left ventricle, which is continually adapting to afterload that changes over a wide range, the right ventricle does not readily compensate for increased impedance to ejection. Therefore, abrupt increases in right ventricular afterload (e.g., air or thromboembolism) are likely to cause catastrophic cardiovascular collapse. Acute dysfunction of cardiac muscle can result from tissue hypoxia, severe sepsis, acidosis, electrolyte disturbance (e.g., hypokalemia), or drug intoxication (e.g., β-blockers). Regardless of the precipitating event, patients with narrowed coronary arteries are particularly susceptible to the adverse effects of a reduced perfusion pressure.

Neural tissue is disproportionately sensitive to reduced blood flow. Circulatory arrest always produces unconsciousness within seconds, and respiratory rhythm ceases rapidly thereafter. Thus, ongoing respiratory efforts indicate very recent circulatory collapse or the continuation of some blood flow, even if below the palpable pulse threshold. (In a person of normal body habitus, a systolic pressure of approximately 80, 70, or 60 mm Hg must be present for a pulse to be consistently detected at radial, femoral, or carotid sites, respectively.)

**CARDIOPULMONARY RESUSCITATION**

Cardiopulmonary resuscitation (CPR) was conceived as a temporary circulatory support procedure for otherwise healthy patients suffering sudden cardiac death. In most cases, coronary ischemia or primary arrhythmia is the inciting event. Since its inception, however, CPR use has been expanded to nearly all types of patients who suffer an arrest. A general approach currently recommended by the American Heart Associated is presented in Figure 20-2. Note that although this approach presents a general overview of intervention for cardiac arrest, specific interventions and situations encountered in the ICU as described in Table 20-1 must be considered. The intensivist is frequently consulted for cardiac arrest occurring on the medical/surgical unit or in clinic spaces of the hospital where this initial approach is applicable. Currently, less than one half of all patients undergoing CPR will be successfully resuscitated initially, and less than one half of these initial survivors live to hospital discharge. Even more discouraging, at least one half of the discharged patients suffer neurological damage severe enough to prohibit independent living. Despite the success portrayed on television, a small number of CPR recipients enjoy even a near-normal postarrest life. In addition, pharmacoeconomic analyses suggest that in-hospital resuscitation may be the least cost-effective treatment delivered with any regularity. The likelihood of successful CPR (discharge without neurological damage) depends on the population to whom the procedure is applied and the time until circulation is restored. Brief periods of promptly instituted CPR are highly successful when applied to patients with sudden cardiac death, but when CPR takes place in the setting of progressive multiple organ failure, the likelihood of benefit approaches zero.

**Principles of Resuscitation**

This chapter emphasizes enduring principles of resuscitation and intentionally omits details that are not based on
convincing evidence or are likely to change. Current expert recommendations for resuscitation are much simpler than those in the past and stress the importance of effective circulatory support and prompt shock of pulseless VT and VF while de-emphasizing respiratory support. Although that advice makes sense for most out of hospital events, in the hospital, the resuscitation team must quickly consider the specific circumstances of each arrest to determine the best course of action (Table 20-1). For example, a mechanically ventilated patient found in VF will not be saved by a formulaic approach to arrhythmia treatment if it is not recognized that the cause of the event is a tension pneumothorax or major airway obstruction. Because survival declines exponentially with time after arrest (Fig. 20-3), most successfully resuscitated patients are revived in less than 10 minutes. To this end, first responders should summon help and begin effective chest compression. If the cardiac rhythm can be monitored and is pulseless VT or VF, unsynchronized direct current (DC) cardioversion using maximal energy should be delivered as quickly as possible. If these initial actions are unsuccessful, more prolonged, “advanced” resuscitation measures may be indicated.
This strategy may be modified based on presenting considerations as listed in Table 20-1. CPR, cardiopulmonary resuscitation; IO, intraosseous; IV, intravenous; PEA, pulseless electrical activity; PETCO₂, end tidal PCO₂; PVT, pulseless ventricular tachycardia; ROSC, return of spontaneous circulation; VF, ventricular fibrillation. (Numbers guide progress through this algorithm.)

Exponential declines in survival result in low success rates after 6 to 10 minutes of full arrest conditions.

The primary activities of resuscitation include (1) team direction, (2) circulatory support, (3) cardioversion/defibrillation, (4) airway management and ventilation, (5) establishing intravenous access, (6) administering drugs, (7) performance of specialized procedures (e.g., pacemaker and chest tube placement), and (8) database access and recording. Managing a cardiopulmonary arrest usually requires several persons to directly execute procedures. Additional personnel are needed for nonprocedural tasks such as documentation, chart review, and communication with the laboratory or other physicians, but limiting the number of people involved to the minimum required avoids confusion.

**Principle 1: Define the Team Leader**

A single person must direct the resuscitation team because chaos often surrounds the initial response. This person should attempt to determine the cause of the arrest, confirm the appropriateness of resuscitation,
establish treatment priorities, and coordinate the steps of ACLS protocol. The leader should also monitor the electrocardiogram (ECG), order medications, and direct the actions of the team members but must avoid distraction from the command role by performing other functions.

**Principle 2: Establish Effective Artificial Circulation**

Blood flow during closed-chest CPR likely occurs by two complementary mechanisms: direct cardiac compression and thoracic pumping. First, compressions generate positive intracardiac pressures, simulating cardiac chamber contraction with the unidirectional heart valves helping to ensure forward flow. In addition, as the chest is compressed, a positive gradient is established between intrathoracic relative to extrathoracic arterial pressures, propelling flow forward. Retrograde venous flow is prevented by jugular venous valves and functional compression of the inferior vena cava at the diaphragmatic hiatus. On relaxation of chest compression, falling intrathoracic pressures promote blood return into the right heart chambers and pulmonary arteries, filling these structures for the next compression. Automated systems are available to provide CPR as other cares or patient transfer occurs (Fig. 20-4).

Regardless of mechanism, even ideally performed closed-chest compression provides only one third of the usual output of the beating heart. Thus, when CPR is performed for more than 10 to 15 minutes, hypoperfusion predictably results in tissue acidosis. If performed improperly, CPR is not only ineffective but potentially injurious. Several points of technique deserve emphasis. Maximal flow occurs with a compression rate of 100 to 120 beats/min. Current recommendations have increased the ratio of compressions to breaths in an attempt to maximize flow. For the same reason, current protocols suggest continuing CPR for several minutes after electrical shock attempts. To optimize cardiac output, it is important to adequately compress the chest. Ideally, the anterior chest is depressed by at least 2 in. in the adult. Timing of the stroke is important: short-duration “stabbing” chest compressions simulate the low stroke volume of heart failure, whereas failure to fully release compression simulates pericardial tamponade or excessive levels of positive end-expiratory pressure (PEEP). Opendest cardiac compression may provide double the cardiac output of the closed-chest technique but presents obvious logistical problems and has not been demonstrated to improve survival.
During CPR, it is difficult to determine whether blood flow is adequate, because pulse amplitude, an index of pressure, does not directly parallel flow and organs vary with regard to the flow they receive at a given pressure. For example, brain flow relates to differences between mean aortic pressure and right atrial pressure, assuming normal intracranial pressure. Therefore, increasing right atrial pressure will decrease brain blood flow when mean arterial pressure is held constant. Coronary blood flow, on the other hand, is best reflected by the diastolic aortic to right atrial pressure gradient. For both, vasoconstrictive drugs (i.e., epinephrine) are recommended to raise the mean aortic pressure.

**Principle 3: Establish Effective Oxygenation and Ventilation**

Establishing a secure airway and provision of supplemental oxygen are essential if the primary problem was respiratory in origin, or whenever resuscitative efforts continue for more than a few minutes. Except in unusual circumstances, ventilation can be quickly accomplished in the nonintubated patient with mouth-to-airway or bag-mask ventilation. Because position, body habitus, and limitations of available equipment often compromise either upper airway patency or the seal between the mask and face, effective use of bag-mask ventilation often requires two people. When the airway is patent, the chest should rise smoothly with each inflation. Gastric distension and vomiting may occur if inflation pressures are excessive. Inflation pressures generated by bag-mask ventilation are sufficient to cause barotrauma and impede venous return; to minimize these risks, breaths should be delivered slowly, avoiding excessive inflation pressures and allowing complete lung deflation between breaths.

In cardiopulmonary arrest, the most common cause of airway compromise is obstruction of the upper airway by the tongue and other soft tissues. Thus, in most cases after effective chest compression and ventilation have been achieved, an experienced person should intubate the airway (see Chapter 6). As a rule, intubation attempts should not interrupt ventilation or chest compression for longer than 30 seconds. Therefore, all materials,
including laryngoscope, endotracheal (ET) tube, and suction equipment, should be assembled and tested before any attempt at intubation. Inability to establish effective oral or bag-mask ventilation signals airway obstruction and should prompt an immediate intubation attempt. When neither intubation nor effective bag-mask ventilation can be accomplished because of abnormalities of the upper airway or restricted cervical motion, temporizing measures should be undertaken while preparations are made to create a surgical airway. The laryngeal mask airway (LMA) is an easily inserted, highly effective temporizing device. It is important to have an LMA, which is appropriately sized for the patient. If the LMA is too large, it may obstruct the larynx or cause trauma to laryngeal structures. An LMA that is too small or inserted improperly may push the base of the tongue posteriorly and obstruct the airway. The LMA should only be used in an unresponsive patient with no cough or gag reflex. If the patient has a cough or gag reflex, the LMA may stimulate vomiting and/or laryngospasm. In unusually difficult circumstances, insufflation of oxygen (1 to 2 L/min) via a large-bore (14- to 16-gauge) needle puncture of the cricothyroid membrane can temporarily maintain oxygenation. Phasic delivery of higher flows of oxygen by the transtracheal route also can promote CO₂ clearance, but CO₂ removal is of much lower priority.

In the arrest setting, direct visualization of the tube entering the trachea, symmetric chest expansion, and auscultation of airflow distributed equally across the chest (without epigastric sounds) are the most reliable clinical indicators of successful intubation. Colorimetric CO₂ detectors attached to the ET tube may support impressions of proper tracheal tube placement; however, because circulation and CO₂ delivery to the lungs are both severely compromised during CPR, detectors may fail to change color on many properly placed tubes. For the same reason, attempts to eliminate CO₂ by ventilation are relatively ineffective.

During CPR, ventilation should attempt to restore arterial pH to near-normal levels and provide adequate oxygenation. Unfortunately, the adequacy of ventilation and oxygenation is difficult to judge because blood gas data are rarely available in a timely fashion. Furthermore, blood gases alone are poor predictors of the outcome of CPR, making their use in decisions to terminate resuscitation of questionable value. The cornerstone of pH correction is adequate ventilation after effective circulation has been achieved—not NaHCO₃ administration. CO₂ in mixed venous blood returned to the lung during CPR freely diffuses into the airway for elimination; however, reductions in pulmonary blood flow profoundly limit the capacity for CO₂ excretion. Consequently, hypocapnia seldom is produced at the tissue level during ongoing CPR. Conversely, excessive NaHCO₃ administration can produce hyperosmolality and paradoxical cellular acidosis. Because exhaled CO₂ measurements reflect the effectiveness of the circulation during CPR, they predict efficiency of compressions as well as outcome. Higher endtidal levels of CO₂ (>10 mm Hg) indicate improved perfusion and portend a better prognosis, whereas persistently low end-tidal CO₂ concentrations (<10 mm Hg) portend a poor prognosis. Failure of a colorimetric CO₂ detector to change color during CPR carries a similarly poor prognosis.

**Principle 4: Establish a Route for Medication Administration**

Access to the circulation must be established rapidly during CPR. Existing peripheral IV catheters are perfectly acceptable for medication administration. When medications are given through peripheral IV lines, they should be followed by at least 20 mL of fluid to facilitate drug entry into the circulation and to prevent mixing incompatible drugs. Central venous catheters (CVCs) reliably deliver drugs directly to the heart, but valuable time should not be wasted inserting a CVC if functioning peripheral venous access exists. (There is also a theoretical concern of delivering very high drug concentrations close to the heart when using a CVC.) Femoral access is less desirable than a jugular or subclavian route because of the higher risk of infection, but is certainly easier to establish without interrupting CPR.
A large intraosseous (IO) needle can be placed very rapidly into the marrow of a long bone, typically the proximal tibia. This IO access is an effective route for drug administration in those patients who do not have a functioning IV. The luxuriant venous plexus of bone provides an efficient conduit to the circulation. There are currently several commercially available stylet/needle devices to rapidly achieve IO access. Typically, the needle penetrates the cortex using a screwing motion until resistance fades. After removal of the stylet, IO positioning is confirmed by aspiration of a small amount of marrow and the ability to gravity-infuse fluid at a slow rate. Major advantages of the IO route include a high success rate for cannulation (>80%), quick insertion (<2 minutes), avoidance of CVC-related complications, and rapid delivery of drug to the circulation. (In experimental models, IO-administered drugs reach the heart in <30 seconds.) Risks are uncommon and predictable. These include nerve or vessel injury, extravasation of drug into soft tissue with necrosis, compartment syndrome, and osteomyelitis.

The intratracheal (IT) route may be used to produce therapeutic drug levels rapidly during resuscitation. Drugs given via the IT route must be delivered with at least 20 mL of fluid to permit most of the dose to access the alveolar compartment, where absorption occurs. The doses of all drugs given by the IT route should be increased at least 2 to 2.5 times than used with IV dosing. The IT route has been demonstrated to be effective for administration of naloxone, atropine, vasopressin, epinephrine, and lidocaine, easily remembered as by mnemonic “NAVEL.” Some commonly used drugs (e.g., norepinephrine, CaCl₂, NaHCO₃) should not be given via the IT route. The first two agents may cause lung necrosis and the third inactivates surfactant.

Intracardiac injections, although dramatic, are rarely necessary, often unsuccessful, and offer no greater likelihood of successful resuscitation. In addition, intracardiac injections are fraught with complications including coronary laceration, pneumothorax, and tamponade. Intramural drug injection may expose the myocardium to massive concentrations of vasoactive drugs, provoking intractable ventricular arrhythmias.

Principle 5: Create an Effective Cardiac Rhythm

As a conceptual guide to treatment, cardiac electrical activity during the arrest can be thought of in two broad categories. The first is the combination of pulseless ventricular tachycardia and ventricular fibrillation (VT/VF), and the second group consists of asystole and pulseless electrical activity (PEA).

Ventricular Tachycardias and Ventricular Fibrillation

VT and VF are the most commonly discovered rhythms in victims of sudden cardiac death. Although VF may be the original arrhythmia, in many cases, the first dysfunctional rhythm is VT, which deteriorates to VF as the heart becomes progressively hypoxic. VT is described as either pulseless or pulse generating. VT without a pulse is treated as VF. VT has been further subclassified as being either monomorphic or polymorphic because there are potential treatment implications for the polymorphic variety. Monomorphic VT is typically a monotonous appearing wide complex tachycardia with a constant axis. Torsades de pointes is the name given to a unique appearing form of polymorphic VT that is frequently associated with baseline prolongation of the QT interval. Torsades is characterized by a constantly changing QRS axis that produces an apparent “twisting of points” about the isoelectric axis (see Chapter 4). Many reversible precipitating factors have been identified, including hypomagnesemia and the use of tricyclic antidepressants, haloperidol, droperidol, type la antiarrhythmics (e.g., quinidine, procainamide, and disopyramide), and quinolone antibiotics (see Chapter 4).

When VT/VF is encountered, the American Heart Association recommends consideration of a standard list of reversible causes including hypovolemia, hypoxia, acidosis, hypokalemia, hyperkalemia, and hypothermia (the “Hs”) to go along with the (“Ts”) tension pneumothorax, cardiac tamponade, toxins, pulmonary thrombosis, and coronary thrombosis. Both VT and VF potentially can be converted with electrical shock, but VF tends to be more
resistant. With VF, the success of cardioversion is influenced by the amplitude of the electrical signal, which correlates inversely with the duration of fibrillation. Success rates vary from less than 5% when low-amplitude VF is the initial rhythm to greater than 30% when coarse VF is the rhythm. When fine VF is shocked, the most likely resulting rhythm is asystole, whereas coarse VF is more likely to be converted to a supraventricular tachycardia or sinus rhythm. Epinephrine is sometimes successful in coarsening a fine VF waveform prior to the attempted shock.

Regardless of whether the initial rhythm is VF, or monomorphic or polymorphic VT, maximal intensity (360 J) unsynchronized monophasic shock should be administered as quickly as possible for all patients in VF and pulseless VT. (Equivalent lower-intensity biphasic [200 J] shocks are equally effective.) For patients receiving open-chest defibrillation, epicardial shocks of 10 to 20 J are almost always sufficient. The goal of delivery for DC countershocks is to abolish all chaotic ventricular activity, allowing an intrinsic pacemaker to emerge. Many defibrillators allow a “quick look” at the rhythm before shock is attempted, but careful inspection of the rhythm is not mandatory before proceeding. Blind cardioversion will not harm adult patients with agonal bradycardias or asystole and should benefit those with pulseless tachycardias or VF. Previous guidelines recommended a series of rapidly delivered, incremental intensity shocks based upon the observations that thoracic impedance declines (but only slightly) with multiple defibrillations and that using a lower electrical dose might reduce defibrillation-induced cardiac damage. Current guidelines recommend simple administration of single shocks. Although all of these approaches have merit, it is clearly more important to restore a circulating rhythm rapidly than to be concerned about potential cardiac electrical injury.

Defibrillators are typically calibrated to discharge through impedance less than that of the adult chest. Therefore, the delivered energy usually is lower than is indicated by the nominal machine settings. This is particularly true in situations, which increase the distance between the paddles and the heart, like morbid obesity and conditions producing high lung volumes (e.g., COPD, large tidal volumes, high PEEP). Improper paddle positioning also dissipates energy and reduces the rate of successful defibrillation. Using the anterolateral technique, paddles are placed at the cardiac apex and just below the clavicle to the right of the sternum. Because bone and cartilage are poor conductors of electricity, paddles should not be located over the sternum. Defibrillator paddles should not be placed over ECG monitor leads, implanted pacemakers or defibrillators, or transcutaneous drug patches, because of the possibility of electrical arcing and equipment damage. Contact between the defibrillator and chest wall should be maximized by use of conducting gels or pads. (Note: Ultrasound gel is a poor electrical conductor.) Standard-sized (8 to 13 cm diameter) paddles on adult defibrillators provide optimal impedance matching between machine and chest wall. If for some reason the defibrillator fails to discharge, ensure that the defibrillator is energized, connected, and correctly set. One rather common reason for failure to discharge during VF is for the machine to be set in the synchronized cardioversion mode. (In the absence of a QRS complex, there is no signal to trigger a “synchronized” discharge of the defibrillator.)

The availability of AEDs has changed defibrillation from an often delayed procedure performed by an expert in a hospital or ambulance to one rapidly accomplished by a novice in a public location. Fortunately, considerable standardization of AEDs has occurred so that regardless of manufacturer, the same basic steps are always used: power on the defibrillator, attach the pads and connect the cables using the illustrations provided, wait for the device to analyze the rhythm and charge, make sure all people are clear of the patient, and then discharge the device if the machine advises to do so.

Pulseless VT or VF that remains resistant to cardioversion after several minutes of effective CPR portends a poor outcome. If initial attempts at defibrillation prove unsuccessful, “coarsening” the rhythm and increasing the vascular tone with epinephrine (1 mg IV, every 3 to 5 minutes) may be helpful. All the while, effective ventilation and chest compression should be maintained. After epinephrine is given, maximum energy defibrillation should
be repeated. When the preceding measures fail, a trial of the antiarrhythmic amiodarone (300 mg IV) may help convert the rhythm when followed by additional shocks.

The small subgroup of patients with torsades deserves special mention. Although torsades is not particularly resistant to cardioversion, the arrhythmia frequently recurs within a short time. For long-term control, discontinuation of potentially precipitating drugs and correction of electrolyte abnormalities are indicated. For patients with a previously normal QT interval, coronary ischemia is a common precipitant amenable to standard treatment. β-Blockers, lidocaine, and amiodarone have all been tried for refractory torsades without any one emerging as a clearly superior agent. For patients known to have prolonged baseline QT interval, MgSO₄ may be helpful, but the most effective measure is to shorten the QT interval, usually by increasing the heart rate (i.e., pacing or catecholamine infusion). In patients with QT prolongation, phenytoin and lidocaine may be tried if the rhythm is refractory to magnesium and cardioacceleration.

Regardless of the initial rhythm, if cardioversion consistently produces any bradycardic rhythm that degenerates to VF, increasing the heart rate with epinephrine, atropine, or pacing can prove useful. (In this situation, overdose of digitalis, calcium channel blockers, or a β-blocker should also be considered.) If countershock produces any tachycardia that repeatedly degenerates to VF or VT, consider the possibility of excessive catecholamine stimulation and decrease infusion rates of adrenergic agents, and/or try administering antiarrhythmics (amiodarone 300 mg IV bolus, procainamide 20 to 50 mg/min IV infusion [with maximum 17 mg/kg or until the QRS duration increases >50%], lidocaine 1 to 1.5 mg/kg IV bolus). Hypokalemia, a frequent contributor to refractory or recurrent VT/VF, is found in approximately one third of all patients suffering sudden death. In this desperate setting, potassium repletion may be considered. Up to 40 mEq of potassium may be administered rapidly. In some cases, the low toxicity compound MgSO₄ may help stabilize refractory VT/VF, but Mg³⁺ levels are unlikely to be measured during the time span of a resuscitative effort and do not correlate well with effects. Thus, it is reasonable to administer MgSO₄ empirically (1 to 2 g over several minutes).

**Asystole and Pulseless Electrical Activity**

For purposes of resuscitation, asystole and PEA are grouped together. Almost any rhythm is preferable to asystole, the complete absence of electrical activity (a flat ECG), but some rhythms (i.e., pulseless slow bradycardia or ventricular escape beats) are not much better. Therefore, a key aim in asystole is to stimulate some electrical activity and then modify that activity to a rhythm with a pulse. Because asystole usually indicates extended interruption of perfusion and carries a grave prognosis, its discovery should prompt serious consideration of whether resuscitative efforts should even begin. It makes no sense to countershock the truly asystolic patient because there is no "rhythm" to modify. However, low-amplitude VF may go unrecognized unless sought using several leads. VF is best detected in leads II and III. Epinephrine (1 mg IV, every 3 to 5 min) given during effective CPR may restore a vestige of electrical activity. Manipulation of electrolyte balance (Ca²⁺, K⁺) also may be useful in specific cases. NaHCO₃ may be useful if severe acidosis, hyperkalemia, or tricyclic antidepressant overdose is the cause of asystole.

PEA, also known as electromechanical dissociation (EMD), is characterized by the inability to detect a pulse despite coordinated ECG complexes. The more common causes of PEA can be easily recalled as a list of conditions beginning with the letters "H" and "T" (Table 20-2). When cardiac in origin, PEA carries a dismal prognosis because it usually is a sign of critical pump failure such as major infarction. A hint to the origin of the problem (cardiac vs. noncardiac) can be gleaned from the width of the QRS complex. Narrow complexes are more likely the result of a noncardiac cause. Mechanical obstruction to the normal transit of blood through the
heart may also cause PEA. Hence, atrial myxoma, mitral stenosis, and critical aortic stenosis may be potential causes. Other reversible conditions that can produce this syndrome include (1) hypovolemia, particularly from acute blood loss (vasopressors lose effectiveness); (2) pericardial tamponade, suspected on the basis of venous engorgement, a history of chest trauma, or preexisting pericardial disease; (3) tension pneumothorax; (4) dynamic hyperinflation (auto-PEEP) from overly zealous ventilation; (5) massive pulmonary embolism by clot or air (thromboembolism may fragment and migrate during CPR, opening the central pulmonary artery and reestablishing effective output; air embolism can be treated by positioning the patient (left side down, Trendelenburg position) and/or transvenously aspirating air from the right heart); (6) hyperkalemia; and/or (7) metabolic acidosis.

As adequate intravascular volume is assured or addressed, epinephrine is given in doses identical to those used for asystole. On the rare occasion when a toxic overdose has resulted in PEA, specific therapy may be available (see Chapter 33). Even though it is becoming much less common, digitalis toxicity deserves mention. A wide variety of arrhythmias are associated with digitalis toxicity including high-grade AV block with bradycardia, junctional tachycardias, and even asystole. Treatment begins by stopping the drug and correcting hyperkalemia and hypomagnesemia. Ca\(^{2+}\) exacerbates the toxicity and should be avoided. Cardioversion (with the lowest effective energy) is indicated if ventricular arrhythmias cause symptomatic hypotension. Phenytoin, lidocaine, and procainamide are useful. Pacing usually is required for high-grade AV block. Use of specific digitalis neutralizing Fab antibody fragment preparations is safe and highly effective if renal function is maintained. Because the Fab-digitalis complex is cleared by the kidney, dialysis may be needed for the patient with renal insufficiency (see Chapter 33).

<table>
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<tr>
<th>Table 20-2. Causes of PEA</th>
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<tbody>
<tr>
<td><strong>Hypovolemia</strong></td>
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<td><strong>Hypoxemia</strong></td>
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<tr>
<td><strong>Hydrogen ions (severe acidosis)</strong></td>
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<tr>
<td><strong>Hyperkalemia or hypokalemia</strong></td>
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<tr>
<td><strong>Hypoglycemia</strong></td>
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<td><strong>Hypothermia</strong></td>
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<tr>
<td><strong>Hyperinflation (auto-PEEP)</strong></td>
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</table>

**Bradycardias**

Bradyarrhythmias that cause sudden death have a poor prognosis. In adults, these rhythms are often a
manifestation of prolonged hypoxemic, hypercarbic respiratory failure and portend asystole (Table 20-3). Indeed, the most important measure to undertake first in treating a patient with hypotensive bradycardia is ensuring adequate oxygenation—not administering sympathomimetic or vagolytic drugs. In general, the slower the rate and the wider the ventricular complex, the less effective the myocardial contraction. The vagolytic action of atropine is most useful in narrow complex bradycardias resulting from sinoatrial node failure or type II or III AV block. Doses of at least 0.5 mg of atropine should be administered and can be repeated up to a total dose of 3 mg. Epinephrine (2 to 10 μg/m) or dopamine

(2 to 20 μg/kg/m) may be helpful for their chronotropic actions. If available, transthoracic pacing can sometimes provide temporary support until definitive transvenous pacing is established or pharmacologic cardioacceleration is achieved. Although useful for symptomatic bradycardia, transvenous ventricular pacing is difficult to achieve in the acute resuscitation situation.

<table>
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<tr>
<th>Table 20-3. Causes of Bradycardia</th>
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<tbody>
<tr>
<td>Hypoxemia</td>
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<tr>
<td>Intense vagal stimulation</td>
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<tr>
<td>β-Blockade</td>
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<tr>
<td>Sinus/atrioventricular node ischemia</td>
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<tr>
<td>Calcium channel blocker use</td>
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<tr>
<td>Drug overdosage (cholinergic effects)</td>
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<tr>
<td>Digitalis</td>
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<tr>
<td>Increased intracranial pressure</td>
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<tr>
<td>Sedative agents (e.g., propofol, dexmedetomidine)</td>
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</table>

**Tachycardias**

Pathologic tachycardia is typically defined as a heart rate greater than or equal to 150 bpm. Absence of a pulse is treated as PEA. The airway should be protected and oxygen provided. End-tidal CO₂ monitoring contributes to evaluation of effectiveness of the rhythm in maintaining perfusion. Symptomatic patients are typically hypotensive with altered mental status, signs of end-organ hypoperfusion, chest discomfort, or heart failure. These individuals should receive synchronized cardioversion. On occasion, adenosine may be therapeutic as well as diagnostic. The first dose of adenosine is 6 mg IV by rapid push with a second dose of 12 mg given later, if required. If the patient has a wide QRS complex (≥0.12 seconds) and is not symptomatic, adenosine may be considered if the rhythm is regular and QRS monomorphic or another antiarrhythmic agent given, such as procainamide, amiodarone, or sotalol. In the patient with a narrow complex QRS, vagal maneuvers and administration of adenosine are appropriate. These patients may also be considered for beta-blockade or a calcium channel blocker.

**Principle 6: Evacuate the Patient to the ICU as Soon as Practical**

When cardiac arrests occur outside an ICU, facilities, equipment, and personnel for resuscitation are less than ideal. On general wards and in public hospital areas, it is often difficult to access the patient, especially if they have fallen alongside a bed or are in a bathroom or elevator. Simply getting emergency equipment to the patient's side can be a challenge in cramped quarters. There is often a crush of unhelpful bystanders and distraught family members, and even the patient's primary caregiver's effectiveness is hindered by their shock from an unexpected arrest. Electrical access and suction capabilities are commonly limited and specialized
equipment, especially for airway management, is not always available. However, the most important limitation of performing resuscitation outside the ICU, especially in a remote part of the hospital (e.g., CT scanner), is that many of the personnel available to help have little experience performing real resuscitations. Preparation of emergency medications and assistance with procedures that are second nature for ICU personnel are often unfamiliar to non-ICU workers. For all these reasons it makes sense to do the absolute minimum required to establish ventilation and a rhythm that produces a pulse, then transport the patient to the ICU.

**Principle 7: Reevaluate and Stabilize**

After arriving in the ICU with a perfusing rhythm with adequate oxygenation and ventilation, it is important to rethink the cause of the arrest, to take measures to prevent recurrence, and to search for resuscitation complications. Tubes and catheters inserted during resuscitative efforts are often suboptimally positioned or are inserted with less than ideal sterile technique. Any intravenous catheter not known to be inserted in a sterile manner should be removed altogether or, if still needed, replaced at a new site using sterile technique. It may be wise to administer a single dose of antibiotic that provides coverage of commonly encountered skin flora (e.g., cefazolin) even though this practice is not evidence based. The position of the ET tube and any chest tubes or CVCs should be confirmed radiographically. (It is extremely common that emergently inserted ET tubes have been advanced into the right main bronchus.) The chest radiograph should also be examined for evidence of resuscitation or procedural injury (e.g., hemothorax or pneumothorax or rib or sternal fractures) and for clues to the cause of the original arrest (mediastinal widening of aortic injury, enlarged cardiac silhouette of pericardial tamponade, pneumothorax) (Table 20-4). The chest film should also be evaluated for the presence of aspiration or pneumonia that may have precipitated the arrest or resulted from it. If there is a suspicion of hemothorax, or hemoperitoneum, or retroperitoneal hematoma, chest and abdominal CT scans are usually diagnostic. However, careful consideration should be given to transporting a recently resuscitated patient outside the ICU; potential benefits should clearly outweigh the risks. If there is suspicion that the arrest may have been precipitated by a neurological event (e.g., ischemic stroke, hemorrhage, tumor, new seizure), it is prudent to obtain a noncontrast head CT scan with the same caveats regarding transport safety. For patients who are not fully awake after resuscitation, the prospect of ongoing seizures should be considered. If a seizure is a reasonable possibility, an electroencephalogram (EEG) should be obtained.

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<th>Table 20-4. Complications of CPR</th>
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<tr>
<td>Rib fractures and cartilage separation</td>
</tr>
<tr>
<td>Bone marrow emboli</td>
</tr>
<tr>
<td>Fractured sternum</td>
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<tr>
<td>Mediastinal bleeding</td>
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<tr>
<td>Liver laceration</td>
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<tr>
<td>Subcutaneous emphysema</td>
</tr>
<tr>
<td>Mediastinal emphysema</td>
</tr>
</tbody>
</table>

Acid-base and electrolyte abnormalities are so common after resuscitation that it makes sense to evaluate a full panel of electrolytes, especially Na⁺, K⁺, Ca²⁺, Mg³⁺, and an arterial blood gas. Because hypoglycemia can cause cardiac arrest, and postarrest hypoglycemia and hyperglycemia can cause or exacerbate brain injury,
rapid determination of blood glucose should be done. If there is suspicion that the cause of the arrest could be medication or toxin ingestion, obtaining a urine or plasma drug screen and specific drug levels (e.g., digitalis, lidocaine, phenytoin) may be enlightening. Although troponin and creatine phosphokinase (CPK) levels are frequently modestly elevated, they rarely provide a definitive diagnosis. Noteworthy elevation of the myocardial band (MB) isoenzyme of CPK is unusual unless repeated high-energy electrical shocks have been delivered. Similarly, after resuscitation, impressive elevation of hepatic (and/or skeletal muscle) enzymes is common but of uncertain significance because frank ischemic necrosis and failure of the liver rarely occur. It is smart to obtain a hemoglobin concentration to search for occult bleeding (e.g., hemothorax from rib fractures or arterial injury, hemoperitoneum from liver or spleen laceration) and to detect anemia that might warrant transfusion. Although elevations of white blood cell counts are routine, they are nonspecific and by themselves should not drive antibiotic use. A decision to obtain lung, blood, or urine cultures should be made on an individual basis, depending on the level of suspicion the role of infection played in the arrest.

It is prudent to obtain a 12-lead ECG in all patients after stabilization to evaluate the rhythm and to look for signs of infarction, ischemia, and electrolyte abnormalities, conduction defects, and preexcitation pathways. The use of antiarrhythmic therapy should be based on an evaluation of the current rhythm and the likelihood of stability (see Chapter 4). If there are questions about valvular competence or stenosis, pericardial fluid, or wall motion abnormalities, an echocardiogram is quite helpful.

Several general recommendations can be made. Finger oximetry should be utilized to maintain oxygen saturation at 94% to 96%. In general, patients should not be hyperventilated and hyperoxia must be avoided. Isotonic fluid should be given judiciously to treat hypotension, defined as systolic blood pressure less than 90 mm Hg. Typical fluids used in this setting are normal saline or lactated Ringers. Vasoactive drugs for the patient requiring catecholamine support are norepinephrine, epinephrine, and dopamine. The patient who is alert and able to follow commands should be monitored closely and further evaluated as described. Where patients cannot follow commands, careful temperature regulation as described below should be emphasized.

Although the primary focus must be on caring for the patient, it is important not to ignore the family and visitors, especially if they witnessed the arrest. Dispatching any free staff member to update the family during the resuscitation and postresuscitation processes can be very effective in allaying fears. In recent years, there has been substantial discussion regarding having family present during resuscitative efforts. This is a very complicated topic, but it is clear that this practice should neither have a blanket prohibition nor absolute requirement. Some family members derive comfort from knowing, by seeing, that all that could be done for their loved one was tried. Other family members suffer terror and revulsion seeing the resuscitation process, which is often unavoidably undignified, unlike stylized popular media portrayals. For these families, a lasting memory of a violent death endures. Unfortunately, there is no reliable way to know how any particular person will react. Because the adverse risk usually outweighs the potential benefit, we do not encourage or advise their direct observation unless asked.

**Principle 8: Preserve the Brain**

Because neurological outcomes in survivors of cardiopulmonary arrest are poor, there has long been interest in methods for cerebral preservation. It should go without saying that maintaining a reasonable perfusion pressure and hemoglobin concentration and saturation are prerequisites for optimal cognitive recovery. The association of worse outcomes associated with hypoglycemia and hyperglycemia suggests that maintaining a normal range of glucose is helpful. There is no evidence to support the routine administration of anticonvulsants, anticoagulants, barbiturates, benzodiazepines, or neuromuscular blockers. Although unproven for this purpose, prevention of excessive cerebral metabolic demand (e.g., suppression of
fever, seizures) makes sense and, particularly with respect to temperature control, is safe and inexpensive. The patient who remains comatose after cardiac arrest should have a temperature maintained in the range of 34°C to 36°C. Perhaps, even more important, is the avoidance of fever. Potential candidates for this targeted temperature management approach should not have active bleeding or significant bradycardia because hypothermia may exacerbate both, as well as cause other complications (see Chapter 28). Therapeutic hypothermia is difficult if not impossible to achieve in waking patients without deep sedation and usually therapeutic neuromuscular blockade to prevent the inevitable, heat-generating shivering. Interestingly, external skin warming (e.g., by air blanket) may effectively block the shiver response as body temperature falls. Servo-regulated intravenous cooling catheters have emerged as the current standard of practice. Regardless of method, the target is a core temperature of 36°C for 12 to 24 hours, with subsequent slow rewarming over 6 to 8 hours.

**Controversies in Resuscitation**

Over the years, advocacy of NaHCO$_3$ and calcium in the resuscitation of arrest victims has waxed and waned; currently, both are assigned low importance. Despite effective artificial support measures, progressive acidosis is an inevitable result of prolonged CPR. When severe, acidosis can render the heart more resistant to defibrillation. However, ventilation is key to pH correction. NaHCO$_3$ is rarely necessary if circulation and ventilation are restored promptly, and no data support its early routine use to improve defibrillation or survival rates. The inability to restore pH toward normal is an ominous sign indicating some combination of failed ventilation and circulatory support. When used, NaHCO$_3$ should be administered cautiously, guided by point-of-care blood gas analysis. An arterial pH ≥ 7.00 usually is adequate for cardiovascular function. However, the appropriate pH target for the arrested circulation is highly controversial. Previously recommended doses of NaHCO$_3$ (1 mg/kg) may produce unwanted side effects, including (1) arrhythmogenic alkalemia, (2) increased CO$_2$ generation, (3) hyperosmolarity, (4) hypokalemia, (5) paradoxical intracellular acidosis of central nervous system (CNS) and myocardium, and (6) a leftward shift in the oxyhemoglobin dissociation curve, limiting delivery of O$_2$ to tissues. Even though the use of NaHCO$_3$ has fallen out of favor, in specific settings (e.g., hyperkalemia with metabolic acidosis, tricyclic antidepressant or aspirin overdose) it can be a useful medication. Because excessive calcium exacerbates digitalis toxicity and the arrhythmic tendency of unstable ischemic myocardium, enhances coronary artery spasm, impairs cardiac relaxation, and may hasten cellular death, its use should be restricted to patients with known hypocalcemia, calcium channel blocker or β-blocker overdose, and hyperkalemia. Calcium forms insoluble precipitates when administered with NaHCO$_3$; hence, the two compounds should not be commingled.

**DECIDING WHEN TO FORGO OR TERMINATE RESUSCITATION**

Certain clinical disorders are associated with a virtually hopeless short-term prognosis (e.g., refractory widely metastatic carcinoma, unremitting multiple organ failure, or severe sepsis), and in such cases, it often is appropriate to decline CPR. Each case must be considered individually with regard to the physical condition of the patient, the wishes of the patient and family (if known), and the likelihood that resuscitation can succeed if performed. CPR is rarely successful if cardiac arrest ensues as the final manifestation of days or weeks of multiple organ failure. The importance of clarifying the “code status” of all seriously ill patients early in the course of an illness should be emphasized. Ideally, the code status is included as part of the admission order set to the ICU. When doubt exists regarding the propriety of resuscitative efforts, CPR should be initiated. A single set of guidelines regarding termination of effort cannot be applied to all clinical situations.

During CPR, neurologic signs and arterial blood gases are unreliable predictors of outcome and should not be used in the decision to terminate.
resuscitative efforts. With that caveat, however, resuscitation seldom is successful when more than 20 minutes is required to establish coordinated ventricular activity. With rare exceptions, failure to respond to 30 minutes of advanced life support predictably results in death. Best results occur when sudden electrical events are corrected promptly with cardioversion. Prolonged resuscitation with a good neurologic outcome may occur, however, when hypothermia or profound pharmacologic CNS depression (e.g., barbiturates) precipitates the arrest.

**PROGNOSTICATION**

CPR frequently fails to deliver the desired result of “discharge alive with normal neurological function.” Resuscitation initially returns circulatory function in approximately 50% of patients to whom it is applied. (The fraction is lower in out-of-hospital cardiac arrests and higher in hospitalized patients, especially those who suffer arrest in the ICU.) Of these early “successes,” approximately 50% survive for 24 hours, but at best, only 25% to 50% of these 24-hour survivors live to hospital discharge. Many survivors suffer neurologic impairment. Downtime greater than 4 minutes before beginning resuscitation, initial rhythms of asystole or bradycardia, prolonged resuscitative efforts, a low exhaled CO$_2$ concentration, and the need for vasopressor support after resuscitation all are adverse prognostic factors. Likewise, poor prearrest health (e.g., severe sepsis, CHF, renal failure), out-of-hospital arrest, and presence of hyperglycemia all are associated with a poor outcome. Interestingly, age alone is not a good predictor of the success of CPR. Long-term survival of severe anoxia is unusual in patients with underlying vital organ dysfunction, perhaps because further organ injury occurs or because neural centers critical to autonomic control and maintenance of protective reflexes are damaged by the event.

The probability of awakening after cardiac arrest is greatest in the first day after resuscitation and declines exponentially thereafter to a very low stable level. (Almost all awakening occurs within 96 hours of resuscitation. Nonetheless, recovery from comatose or vegetative states has been reported after 100 days.) Targeted temperature management also appears to prolong the interval of observation necessary to confidently assign prognosis. Surprisingly, the clinical examination is a better predictor of neurologic recovery than any imaging or laboratory test. Absence of pupillary and corneal responses at or beyond 72 hours, especially if there is no motor response or extensor posturing, is a powerful predictor of a poor outcome. Similarly, myoclonus or status epilepticus within the first day following arrest predicts poor outcomes. Although an EEG is very useful for care if it demonstrates seizures, EEG activity is suppressed by sedatives, anticonvulsants, and hypothermia making the test an insensitive predictor of outcome. CT or MRI of the head may show perfusion-related abnormalities or cerebral edema following CPR that may support the clinical assessment. However, unless such abnormalities are profound, used alone they are unreliable predictors of eventual outcome.

**SUGGESTED READINGS**


• Key Points

1. In ischemic heart disease, survival and ventricular function are maximized by rapidly reestablishing sufficient myocardial blood flow to prevent myocardial necrosis. Percutaneous coronary intervention is the reperfusion modality of choice, but if there are substantial delays in transfer to the cath suite, then fibrinolytic therapy should be used in lytic-eligible patients. The door-to-balloon time should be less than 90 minutes.

2. Reducing myocardial oxygen consumption by limiting heart rate (avoidance of exercise and judicious use of β-blockade), reducing afterload (controlling hypertension and normalizing ventricular filling pressures), and alleviating excessive catecholamine stimulation are important steps to optimize myocardial supply and demand.

3. Myocardial oxygen supply can be quickly and simply boosted with nitrates, restoring normal oxygen saturation and optimization of hemoglobin concentration.

4. Most patients should receive agents to interrupt the clotting cascade, as well as oxygen (when needed), pain relievers, and β-blockers in those without signs of ventricular insufficiency. All suitable candidates should be considered for immediate interventional procedures (angioplasty/stent) or for antithrombotic therapy. The presence of ST segment elevation and the duration of chest pain prior to arrival have a direct bearing on the value of thrombolytics and interventional catheterization.

5. After stabilization has been achieved, an angiotensin-converting enzyme inhibitor and high-dose statin should be considered to minimize the risk of lasting ventricular dysfunction.

NON-ST ELEVATION ACUTE CORONARY SYNDROMES: UNSTABLE ANGINA AND NON-ST ELEVATION MYOCARDIAL INFARCTION

Definitions and Pathophysiology of Acute Coronary Syndrome

Unstable angina (UA) and non-ST segment elevation myocardial infarction (NSTEMI) are now grouped under the heading of non-ST elevation acute coronary syndromes (NSTE-ACSs). Because they share a common underlying pathophysiology, the management of these two conditions is quite similar. UA is synonymous with the terms preinfarction angina, crescendo angina, intermediate coronary syndrome, and acute coronary insufficiency. NSTEMI implies non-Q wave myocardial injury. The main difference between UA and NSTEMI is that biomarkers of myocardial necrosis are elevated in the latter (e.g., creatine kinase-myocardial band [CK-MB], troponin-I, troponin T).

Myocardial ischemia results from an imbalance between oxygen supply and demand. Anginal chest pain is the clinical expression of this imbalance. Because the left ventricle (LV) comprises most of the cardiac muscle mass and faces the greater afterload, it is at higher risk for ischemia. Myocardial oxygen delivery may be limited by (1) coronary atherosclerosis, (2) plaque rupture with thrombosis, (3) coronary artery spasm, (4) anemia, (5) hypoxemia, (6) limited diastolic filling time (tachycardia), and (7) hypotension.

Four major factors increase cardiac oxygen demand: (1) tachycardia and/or increased systemic
metabolic demands for cardiac output, (2) heightened LV afterload causing increased transmural wall tension (e.g., hypertension, LV cavity dilation, aortic stenosis), (3) increased LV mass (hypertrophy), and (4) increased contractility. Despite the predisposition of the LV to ischemia, conditions that cause hypertrophy, dilation, or increased afterloading of the right ventricle (RV) also can put its muscle mass at risk. For example, pulmonary embolism may precipitate RV ischemia—a phenomenon that is most common in patients with underlying right coronary artery (RCA) narrowing or cor pulmonale.

Instability of a coronary atherosclerotic plaque is the key to the pathophysiology of ACS and infarction. Degree of coronary narrowing plays a secondary role. Histologic studies of coronary vessels have shown that atherosclerotic plaques are intimomedial in location. In general, there are two types of coronary plaques: (1) stable plaque with small lipid core and thick fibrous cap and (2) unstable plaque with large lipid core and thin cap. The former generally causes stable angina pectoris if it causes significant obstruction of the vessel (>50% to 70% of the vessel lumen diameter). Soft, lipid-laden plaques with thin caps are more prone to rupture, promote local clotting, and provoke ACS. Many of these plaques do not cause significant obstruction of the lumen of coronary vessels before the onset of the ACS. Hence, the patient may not have experienced any cardiac symptoms prior to the onset of ACS even with exercise, and stress tests may be negative.

Acute instability and rupture of one or more coronary plaques with superimposed thrombosis are central to the pathophysiology of ACS. This clot, composed of platelets and thrombin, not only produces a fixed vessel occlusion but also stimulates reversible vasoconstriction. The resulting sudden coronary artery occlusion, which may be total or subtotal, causes acute myocardial ischemia or infarction. UA represents a high-risk transition period during which most patients undergo accelerated myocardial ischemia. If unchecked, this transition culminates in acute myocardial infarction (AMI) or sudden cardiac death (SCD) in up to 15% of patients within just a few weeks. Coronary angiography in many of these patients demonstrates complex coronary plaque lesions with varying degrees of superimposed thrombosis. Intravascular ultrasonic examination of coronary vessels (IVUS) is another useful tool that has helped shed considerable light, not only on the pathophysiology but also on the management of coronary artery disease (CAD), particularly in the setting of ACS.

The key role of platelets in the pathophysiology of ACS has undergone considerable review in the past decades. Platelet activation and aggregation encourage formation and propagation of a plateletrich or “white” clot over a ruptured atherosclerotic plaque in patients with UA and NSTEMI. This contrasts with the fibrin-rich or “red” clot seen in the coronaries of patients with STEMI. The current recommendations on the use of antithrombin and antiplatelet therapies in NSTEMI and that of fibrinolytic therapy in patients with STEMI derive not only from the pathophysiology of these conditions but also from the results of informative clinical trials performed within the last two decades.

Diagnosis

**History and Physical Examination**

The term **UA** denotes new pain or a departure from a previous anginal pattern. UA occurs at rest or with less provocation than stable angina. Pain lasting longer than 15 minutes also suggests UA. Angina occurring in the early post-MI period or within weeks of an interventional coronary procedure also is best termed “unstable.” Commonly, the pain is described as a “tightness,” “heaviness,” or “squeezing” in the substernal region. UA may awaken patients from sleep or present as pain at a new site such as the jaw or arm. Elderly, female, and diabetic patients are more likely to experience atypical symptoms, pain intensity, and distribution. Although the classical description is one of heavy central chest pressure radiating to the jaw and left arm, it is rational to raise suspicion of UA or evolving MI in patients reporting acute pain from “nose to navel.” Autonomic manifestations (nausea, vomiting,
tachycardia, or sweating) also favor “instability.” Blood pressure frequently rises before the onset of pain, even in resting patients. Rising blood pressure boosts afterload, increasing wall tension and myocardial O\textsubscript{2} consumption. Less commonly, the abrupt onset of dyspnea and congestive heart failure (CHF) may be the only manifestation of UA.

**Data Profile**

**Electrocardiographic Changes**

Electrocardiographic patterns are invaluable in determining the presence of coronary occlusion and in guiding the nature and urgency of therapeutic intervention. During episodes of ischemic chest pain, electrocardiogram (ECG) features may include (1) ST segment elevation or depression, (2) T wave flattening or inversion, (3) premature ventricular contractions (PVCs), or (4) conduction disturbances, including bundle-branch block (Fig. 21-1). Q waves often but not invariably indicate completed infarction. ST segment elevation strongly correlates with fresh coronary occlusion (STEMI), whereas ST depression in association with or without T wave inversion indicates ischemia without acute coronary luminal occlusion (non-STEMI or NSTEMI). Perhaps only 20% to 25% of ACS syndromes are STEMI.

Reversible ST depression or T wave inversion is detectable in most affected patients if continuous ECG monitoring is used, a finding that may not emerge during a single 12-lead ECG. Even with intensive monitoring, ECG findings are absent in up to 15% of symptomatic patients with UA. Therefore, a normal ECG does not exclude a diagnosis of UA or MI. Conversely, it has been estimated that up to 70% of all ECG-documented episodes of ischemia are clinically silent.

**Cardiac Enzyme Markers**

Elevated total CK (including the CK-MB fraction) and cardiac troponins (I and T) are markers of myocardial necrosis and indicate an MI, even in the absence of convincing ST segment-T wave changes. Troponins (I/T) are more sensitive and specific in making the diagnosis of an AMI than is CK-MB. Their rise may be delayed 1 to 3 hours after onset, so that their absence at a very early stage does not exclude an ongoing AMI. Once present, elevations are often detected for 10 days or longer, especially in patients with renal insufficiency. Troponin elevation in NSTE-ACS correlates with adverse prognosis. These are also patients who are likely to benefit from aggressive antiplatelet regimens and from early coronary angiography and revascularization. Highly sensitive C-reactive protein (hs-CRP) levels are also increased in patients with ACS. ACS patients with the highest levels of hs-CRP and troponins have the worst prognosis.

![FIGURE 21-1. Electrocardiographic evolution of AMI. SEMI, subendocardial (nontransmural) MI.](image-url)
Prognostic Factors
Patients with UA have a lower short-term mortality rate (2% to 3% at 30 days) compared to those with acute NSTEMI (5% to 7% at 30 days). The in-hospital or short-term mortality of patients with STEMI is higher compared with those with NSTEMI (6% to 9% vs. 5% to 7% at 30 days). However, the long-term mortality in NSTEMI (10% to 12%) is similar to or greater than that associated with STEMI (9% to 11%), likely because of their greater incidence of multivessel CAD.

Thrombolysis in Myocardial Infarction Risk Score
Several risk variables have been identified in patients with NSTE-ACS. A value of 1 has been assigned to each risk variable, and the total score has been shown to bear a linear relationship with risk of adverse events (death, MI, recurrent ischemia, and need for urgent revascularization) in the short term. The variables are (1) age greater than or equal to 65 years, (2) prior coronary stenosis greater than or equal to 50%, (3) presence of greater than or equal to three coronary risk factors, (4) ST segment deviation on admission ECG, (5) elevated cardiac biomarkers, (6) greater than or equal to two anginal episodes in the last 24 hours, and (7) prior use of aspirin (marker for vascular disease). The adverse event rate is 4% to 5% for thrombolysis in myocardial infarction (TIMI) risk score of 0 to 1 but approaches 40% for those with score of 6 to 7. Elevated levels of hs-CRP indicate a worse prognosis in each TIMI scoring category.

Management of NSTE-ACS
Patients with NSTE-ACS should be monitored closely and should receive aggressive antithrombotic, antiplatelet, and antianginal treatments (Fig. 21-2). Most patients with UA can be stabilized with appropriate medical therapy. Although the immediate urgency of STEMI-ACS is attenuated, coronary angiography and revascularization procedures have become increasingly popular in the treatment of these patients over the course of the last decades. Emergent coronary angiography and revascularization procedures are uncommon for NSTE-ACS patients, but most are advised to undergo coronary angiography and possible revascularization within a few days of admission to the hospital. Coronary revascularization procedures include either percutaneous coronary interventions (PCIs) (PTCA and stenting) (Fig. 21-3) or coronary artery bypass graft (CABG) surgery. Essentially, only patients with contraindications for invasive cardiac procedures are treated by noninvasive medical management alone. Thrombolytics are not advisable in most (nonocclusive) NSTE-ACS because “red thrombus” is not present and because thrombolytics have procoagulant properties. Apart from considerations relating to coronary patency, the two basic principles in the treatment of UA are to reduce myocardial O\textsubscript{2} demand and improve O\textsubscript{2} supply.
Reducing Myocardial Oxygen Consumption

The principal measures to decrease myocardial oxygen consumption are to limit heart rate and afterload. These goals are immediately accomplished by curtailing physical activity with bed rest. Exercise stress tests are contraindicated in unstable patients because frank infarction may ensue. Arrhythmias like atrial fibrillation (AF) and sinus tachycardia should be controlled, both to reduce $O_2$ consumption and to optimize diastolic filling time, thereby maximizing the sufficiency of coronary perfusion. Controlling hypertension and CHF decreases myocardial wall tension and therefore facilitates perfusion (see Chapter 22). Situations that increase heart rate (anxiety, use of short-acting nifedipine) or both heart rate and total body oxygen consumption (e.g., thyrotoxicosis, alcohol withdrawal, stimulant drug intoxication, anxiety, agitation, infections, etc.) should be promptly recognized and corrected. $\beta$-Blockers effectively reduce myocardial oxygen consumption by decreasing heart rate and cardiac contractility and improve $O_2$ supply by lengthening diastolic filling time. $\beta$-Blocking drugs are particularly useful in reducing oxygen consumption in the tachycardic and hypertensive patient with UA and ACS but are contraindicated in acute heart failure, coronary artery spasm, or severe bronchospasm. Selective $\beta$-blocking agents such as carvedilol may be used cautiously in patients with modestly impaired ejection fractions and tachycardia, but, in general, should be withheld until stability is achieved.
Increasing Myocardial Oxygen Supply

The most important treatments under this category are the strategies for myocardial revascularization, which include percutaneous coronary angioplasty, coronary stenting, and coronary artery bypass surgery (dealt with later in this chapter). Myocardial oxygen supply can also be increased simply by boosting hemoglobin saturation or elevating hemoglobin concentration to levels higher than 9 g/dL, in severely anemic patients.

Pharmacotherapy is also necessary to optimize myocardial perfusion. Nitroglycerin (NTG) is used commonly and may be administered sublingually, orally, transcutaneously, or intravenously. (For unstable patients, the intravenous route is most easily regulated and reliable.) In addition to dilating coronary vessels, NTG also decreases wall tension of the LV by reducing preload and, to a lesser extent, afterload. Acting through these mechanisms, NTG also reduces the risks of life-threatening arrhythmias in acute ischemia. Nitrates are effective both for classical and variant angina because of their direct coronary vasodilating properties. NTG is titrated to relieve chest pain or to reduce blood pressure by 10% to 20%. Usually, intravenous doses of 0.7 to 2.0 μg/kg/min suffice. Intravenous NTG usually is begun at 5 to 15 μg/min and titrated upward as necessary in increments of 5 μg/min every 5 minutes up to a maximum dose of 200 μg/min. Headache is a common side effect but usually responds to simple oral analgesics. When the dose is excessive or the patient is dehydrated, hypotension and reflex tachycardia result from NTG-induced vasodilation. These adverse effects usually can be offset by volume expansion or α-agonist therapy. Because ethanol is used as a vehicle for NTG infusions, violent adverse reactions may occur in those rare patients taking Antabuse. Obviously, use of high doses of NTG for prolonged periods may also produce alcohol intoxication. Within 48 to 72 hours of initiating NTG therapy, tolerance is often observed, necessitating higher infusion rates. Seldom seen problems induced by NTG therapy include increased intraocular and intracranial (IC) pressures and methemoglobinemia.

Coronary spasm, a major contributor to myocardial ischemia provoked by the irritating products of plaque rupture, may be ameliorated by nitrates or calcium channel blockers. Blockers of slow calcium channels (e.g., nifedipine, nicardipine, and amlodipine) can be rapidly effective in reversing coronary spasm. In UA, these drugs should be viewed as adjuncts to nitrate, β-blocker, and antithrombotic therapy. Because calcium antagonists have vasodilating, negative inotropic, and positive chronotropic actions, they may not always be well tolerated. If coronary vasodilating effects predominate, myocardial oxygen supply-demand balances benefits. Conversely, if systemic vasodilation, hypotension, and reflex tachycardia predominate, myocardial oxygen demand can outstrip supply and ischemia can worsen. Therefore, caution must be exercised to avoid...
hypotension or excessive tachycardia when using calcium channel antagonists.

**Antiplatelet Therapy**

**Aspirin**

Most patients with NSTE-ACS have an ulcerated atherosclerotic plaque covered by a subocclusive accumulation of platelets, thrombin, and red blood cells. Typically, these patients have platelet-rich or “white clot.” Therefore, aggressive antiplatelet therapies are indicated in stabilizing them. Aspirin (162 to 325 mg daily) should be initiated immediately for all patients with ACS unless compelling contraindications exist. Cyclooxygenase-1 (COX-1)-mediated platelet aggregation is inhibited within 15 minutes when non-enteric-coated tablets are chewed and swallowed. Aspirin reduces synthesis of both thromboxane A2 (TXA-2) and prostacyclin. TXA-2 is a powerful promoter of platelet aggregation. Prostacyclin, on the other hand, promotes vasodilation and inhibits platelet aggregation. Low-dose aspirin preferentially inhibits TXA-2 synthesis, and endothelial prostacyclin synthesis is inhibited by high-dose aspirin. In the VA cooperative study, Canadian multicenter trial, and RISC trial, aspirin was found to reduce the risk of death and AMI by approximately 50% in patients with NSTE-ACS. In a large meta-analysis by the Antithrombotic Trialist's Collaboration, aspirin reduced risk of death, MI, and stroke by about 46%. The benefits of aspirin may persist for years with continued therapy. The risk of recurrent events is reduced by at least 25%. The risk of coronary reocclusion after PCIs is reduced by about 50% with use of aspirin. At the low doses (75 to 150 mg) needed for platelet inhibition, few hemorrhagic or gastrointestinal side effects occur. At a lower dose, aspirin caused 2.5% major bleeds with 1% requiring transfusions. Aspirin resistance is seen in about 5% to 10% of patients, and these individuals are at increased risk for cardiovascular events. Although inhibition of platelet aggregation may complicate subsequent coronary artery surgery, aspirin-related clotting defects are reversible with platelet transfusions. Dipyridamole does not enhance the protective effect of aspirin in coronary ischemia, but clopidogrel and ticlopidine do complement the anti-ischemic effect of aspirin.

**Clopidogrel, Ticlopidine, and Prasugrel**

These agents, which are used in conjunction with aspirin for dual antiplatelet therapy, belong to the thienopyridine class. They prevent platelet aggregation by noncompetitive inhibition of the adenosine diphosphate (ADP) binding to the type 2 purinergic (P2Y12) receptor, thereby inhibiting the activation of the glycoprotein IIb/IIIa receptor complex. Because ticlopidine requires 3 to 6 days of therapy for full antiplatelet effect and carries small but noteworthy risks of neutropenia (2.5%) and thrombotic thrombocytopenic purpura-hemolytic uremia syndrome (TTP-HUS), it has been replaced by safer and effective ADP receptor agents, such as clopidogrel.

Clopidogrel has been extensively studied in patients with ACS and in those who have received intracoronary stents. The life-threatening adverse effects seen with ticlopidine are far fewer with clopidogrel. In the CURE trial, clopidogrel use in ACS was found to significantly reduce risk of cardiovascular events (mostly reinfarctions) compared to aspirin alone. The usefulness of clopidogrel as an agent in reducing risk of cardiovascular events in patients who have received coronary stents has been clearly demonstrated in the PCI-CURE and CREDO trials. Clopidogrel is usually given as an oral bolus of 300 mg, followed thereafter at a dose of 75 mg once daily. The antiplatelet effects of clopidogrel are seen within hours. Significant blood levels may be achieved sooner with a larger bolus dose of the medication (600 or 1,200 mg). Along with ASA (81 mg once daily), it is given for a month after the implantation of bare-metal coronary stents and for at least 3 to 6 months after insertion of drug-eluting coronary stents. In patients with ACS, clopidogrel can be continued for 9 to 12 months. In some individuals at high risk for future cardiovascular events, clopidogrel with low-dose aspirin may be continued indefinitely if there are no contraindications and if cost is not an issue. There is a slight but significant increase in risk of bleeding with combination of clopidogrel and aspirin (3% to 5% risk of major bleeding), particularly in the elderly.
Prasugrel and ticagrelor are recently introduced oral thienopyridine ADP receptor antagonists available for patients with ACS. They are both more powerful antiplatelet agents than clopidogrel and achieve platelet-inhibiting effects more quickly.

Ticagrelor is a relatively reversible agent, whereas the effects of both clopidogrel and prasugrel linger for days. Although potency is an advantage of prasugrel, it comes at the cost of higher incidence of bleeding complications. Although their ultimate place is as yet undetermined, these newer agents reduce the incidence of stent thrombosis and have been trial-determined to reduce the likelihood of recurrent ischemic events. They may be a good option for those who present with stent thrombosis with clopidogrel, in those with multiple drug-eluting stents, and in those at less risk of bleeding (like the younger patient population).

**Glycoprotein 2b/3a Receptor Inhibitors**

Gp2b/3a receptor inhibitor agents are the most powerful intravenous form of antiplatelet agents available. The Gp2b/3a receptor binds to fibrinogen, which actually forms the molecular link that bridges adjacent platelets in the process of platelet aggregation. By binding to the Gp2b/3a receptors, these agents inhibit binding of fibrinogen to this receptor and thus inhibit platelet aggregation. Although the use of these agents in ACS management had surged in prior years, their use presently is more restricted, as precatheterization treatment with dual antiplatelet therapies has become more common and bivalirudin now displaces heparin as an antithrombotic in the catheterization laboratory. There are two broad classes of these agents: (1) large-molecule agents like abciximab (ReoPro) and (2) small-molecule agents (peptide-like eptifibatide [Integrilin] and non-peptide-like tirofiban [Aggrastat]). Because abciximab molecules bind irreversibly to the Gp2b/3a receptor and produce permanent noncompetitive platelet inhibition, the clinical effects of the medication can last for 7 to 10 days. Severe uncontrolled bleeding associated with abciximab should be addressed by stopping the medication and transfusing platelets. The small-molecule agents bind reversibly to the Gp2b/3a receptor to produce competitive platelet inhibition. The antiplatelet effects usually reverse within 4 to 6 hours of stopping the medication. Platelet transfusions should not be given for bleeding provoked by small-molecule Gp2b/3a receptor antagonists, as transfusion inhibits new platelet formation.

The risk of major bleeding with Gp2b/3a receptor antagonists is 2.5% to 4.0%. Most of the bleeding experienced from these agents is from vascular access sites after PCI. Severe thrombocytopenia with counts less than 50,000/mm$^3$ occurs in 0.5% to 1.5% of patients who receive abciximab. Because thrombocytopenia can develop within hours of initiating an abciximab infusion, it is prudent to check platelet counts within 4 hours of starting the infusion and again at the end of the infusion. Severe thrombocytopenia is rare with small-molecule agents (tirofiban and eptifibatide). There is also a small chance (0.5% to 1.0%) of developing serious pulmonary hemorrhage with abciximab therapy. This potentially fatal condition is rarely if ever encountered with the small molecular weight Gp2b/3a receptor antagonists. Catheterization laboratory practices currently favor the use of bivalirudin (a direct thrombin inhibitor [DTI]) over the customary heparin plus GP2b/3a inhibitor strategy during the procedure and immediate postprocedure phases. Although of equivalent efficacy to the latter combination, bivalirudin has been demonstrated in large clinical trials to be associated with lower bleeding risk. High cost may be a factor that limits its use in some environments.

**Antithrombotic Therapy**

**Unfractionated Heparin**

Adequate doses of intravenous heparin given urgently along with oral aspirin reduce mortality and morbidity in patients with ACS by immediately interrupting the process of clotting on the coronary endothelium. The
combination of heparin and aspirin is superior to aspirin alone in preventing the early complications of UA. Superiority of the combination probably results from the different mechanisms of the two treatments: heparin inhibits soluble clotting factors and thrombin mediated platelet aggregation, whereas aspirin inhibits COX-mediated platelet aggregation. Even though the addition of heparin to aspirin raises the bleeding incidence slightly, the risk-benefit ratio almost always favors combination therapy. The goal of heparin therapy is to rapidly achieve and maintain a partial thromboplastin time (PTT) of 1.5 to 2.0 times the patient's baseline or laboratory control value. This goal is best achieved using an intravenous bolus (60 units/kg, with a maximum dose of 4,000 units), followed by a continuous intravenous heparin infusion at a rate of 12 units/kg/h (maximum 1,000 units/h). The heparin infusion should be continued until coronary revascularization. Today, most of the ACS patients receive an intravenous infusion of a Gp2b/3a receptor antagonist for 12 to 24 hours after PCI. They are also typically on aspirin and clopidogrel long term after PCI. In patients who are candidates for coronary bypass surgery, heparin and aspirin should be continued until surgery. In patients who are not candidates for coronary angiography and revascularization, heparin should be continued for 3 to 5 days. There is a risk of rebound angina when the heparin infusion is stopped. Thereafter, long-term use of aspirin alone can result in a 50% reduction in the incidence of angina recurrence.

Unfractionated heparin (UFH) is a hetereogenous mixture of polysaccharides with molecular weights ranging from 3,000 to 30,000. There are several disadvantages with UFH. The antithrombin binding sites of heparin can be bound by a number of other plasma proteins, by platelet factor 4, and also by endothelial cells, thereby diminishing its therapeutic effect. Furthermore, heparin does not bind to clot-bound thrombin and to factor Xa bound to platelets inside a clot. Thus, there is the possibility of clot propagation while the patient is receiving heparin. Heparin-induced thrombocytopenia (HIT) is another serious adverse effect. Perhaps surprisingly, in this ACS setting, the currently available low molecular weight alternatives may be more effective in selective categories but have not been shown to offer dramatic risk-benefit advantages across the entire “at-risk” population.

Low Molecular Weight Heparins

These are homogenous glycosaminoglycans with molecular weight ranging from 4,000 to 6,000. Low molecular weight heparins (LMWH) have greater anti-factor Xa activity and less anti-factor IIa activity as compared to UFH. They act mainly by preventing thrombin generation and have lesser effect on a PTT as compared to UFH. Assays measuring anti-factor Xa activity are now in widespread use. Enoxaparin is the most popular of all LMWH that has been shown to be efficacious in patients with NSTE-ACS, as in acute pulmonary embolism and deep venous thrombosis. Enoxaparin has been reported in clinical trials to hold a modest advantage over UFH in reducing cardiovascular events, with risk of death, recurrent ischemia, and MI. Benefit appears more pronounced in patients with high risk features like troponin elevation and those with higher TIMI risk scores.

In patients with ACS who have creatinine clearance greater than 30 mL/min, enoxaparin is used in the dosage of 1 mg/kg subcutaneously twice daily. There is little need to monitor the clotting parameters because the therapeutic effect is quite consistent and predictable. The anticoagulant effect with enoxaparin is consistent because of very little binding to plasma proteins, endothelial cells, and macrophages. When thought advisable, as in massively obese patients, anti-factor Xa activity can be monitored. Enoxaparin’s risk of thrombocytopenia is quite low. Major bleeding is also uncommon, but the risk may be higher in the elderly and those with renal failure. In patients requiring CABG, the drug should be stopped 12 to 24 hours prior to the operation. In patients undergoing cardiac catheterization and PCI, there is always a concern for bleeding because of concomitant use of UFH, Gp2b/3a receptor antagonists, and clopidogrel. The following rule of thumb can be used for heparin dosing in patients needing PCI: within 8 hours of having received a dose of enoxaparin, no additional UFH is needed for PCI; between 8 and 12 hours, use UFH at dose of 25 to 50 units/kg; and if greater than 12 hours
after receiving enoxaparin, use 50 to 70 units/kg of UFH. Despite its proven efficacy, only a minority of patients in North America and 50% of patients in Europe receive LMWH for ACS.

Direct Thrombin Inhibitors

The direct thrombin inhibitor (DTI) agents available are hirudin, lepirudin (recombinant hirudin), argatroban, and bivalirudin. These agents are substantially more expensive than UFH and enoxaparin. They are powerful anticoagulants and their anticoagulation effect is consistent and predictable. DTIs do not depend on antithrombin III for their activity. They bind to thrombin (factor IIa) and thus inhibit coagulation process. Because thrombin is also a powerful platelet activator, DTIs also inhibit platelet activation. In a large meta-analysis, DTIs were shown to reduce rates of recurrent ischemia and infarctions as compared to heparin in patients with NSTE-ACS, but their use was associated with increased incidence of major bleeding requiring blood transfusions. DTIs are currently only recommended for ongoing use in those with HIT. However, the use of bivalirudin in the setting of coronary intervention has dramatically increased, ever since the REPLACE-2 trial showed significantly reduced procedure-associated bleeding rates compared with heparin and Gp2b/3a receptor antagonists. This drug, though expensive, has become popular with interventional cardiologists.

Fibrinolytic Therapy

There is no proven benefit of fibrinolytic therapy in NSTE-ACS. This is probably because a completely occlusive coronary thrombus is present in fewer than 50% of patients, because platelet-rich thrombi, which predominate in coronary vessels of patients with NSTE-ACS, are resistant to dissolution with fibrinolytic therapy and because fibrinolitics promote platelet aggregation. Fibrinolytic agents have not been demonstrated to be effective in reducing the risk of MI or death in NSTE-ACS and in fact may be deleterious. This is in stark contrast to STEMI-ACS, where the effectiveness of fibrinolytic therapy has been proven. Therefore, fibrinolitics are contraindicated in NSTE-ACS, except in unusually high-risk and unstable patients as a temporizing measure during transport to a center where PCI is available.

Invasive Strategy of Coronary Angiography and Percutaneous Coronary Intervention

Several recent studies have demonstrated benefit with an early invasive strategy in patients with NSTE-ACS as compared to conservative treatment strategy. In the early invasive strategy, patients undergo coronary angiography and revascularization within 12 to 48 hours of presentation to the hospital with ACS. In the conservative strategy, patients undergo coronary angiography only for significant recurrent ischemia or ischemia demonstrated by stress testing. The early invasive strategy results in lower short-, intermediate-, and long-term major cardiac event rates (death, MI, recurrent ischemia, and revascularization rates) and shorter lengths of stay in the hospital. This is particularly true in patients with high-risk characteristics like elevated serum cardiac biomarkers (like troponins), ongoing chest discomfort, and dynamic ST-T changes on ECG. In intermediate-risk patients, a conservative strategy may be as good as an early invasive strategy. In low-risk patients, a conservative strategy is preferred.

It has been shown that use of aggressive medical regimens including “upstream” use of Gp2b/3a receptor antagonist (e.g., tirofiban or eptifibatide) for 12 to 24 hours before PCI reduces the risk of MI or death after PCI by at least 30% to 40%. The majority of patients with NSTE-ACS will be candidates for PCI after coronary angiography (70% to 80%). Compared to balloon angioplasty, coronary stenting appears to substantially reduce recurrent ischemia and infarction. Restenosis in 3 to 6 months is a major limitation with bare-metal stents and occurs because of an intimal hyperplasia reaction to the vessel wall injury. Widespread use of drug-eluting stents has reduced long-term restenosis and repeat revascularization rates by 50% to 70%. However, with current
stents, these patients must remain on longterm clopidogrel and aspirin therapy.

Emergent cardiac catheterization and revascularization in NSTE-ACS are needed less commonly. The indications include pulmonary edema, hypotension, and malignant ischemic ventricular arrhythmias. Most of the other high-risk patients can be stabilized with medical management for 12 to 48 hours before angiography and revascularization.

**Coronary Bypass Graft Surgery Versus Stenting**

The mortality risk with urgent CABG in NSTE-ACS patients is around 4% to 5%. The other complications of bypass surgery include stroke and cognitive abnormalities. This is mainly due to cross-clamping of the aorta and the use of cardiopulmonary bypass. These risks should be borne in mind, especially while operating on elderly patients. The complications and recovery times have improved over the course of the two decades because of refinement in surgical techniques and postoperative care. The advent of left internal mammary artery (LIMA) grafting to the left anterior descending (LAD) artery was a major advance in bypass surgery since the 1980s. The use of off-pump bypass surgery may reduce the risk of stroke in elderly patients. The usual length of stay in the hospital is 5 to 7 days, but it may take up to 2 to 3 months for the patients to recover back to their usual pre-event baseline.

Only 20% to 30% of NSTE-ACS patients need urgent CABG. The classical indications for CABG include (1) significant left main coronary stenosis, (2) multivessel CAD with left ventricular ejection fraction (LVEF) less than 40%, (3) CAD with significant valvular disease (aortic stenosis and mitral insufficiency), (4) diabetes mellitus with multivessel CAD, (5) coronary anatomy unsuitable for PCI, and (6) failed PCI. It is preferable to stabilize these patients with medical management prior to CABG. Sometimes, an intra-aortic balloon pump (IABP) may be needed for prior stabilization in patients with hypotension, CHF, and LV dysfunction. However, with the ever-expanding capabilities of interventional cardiology, many of the patients who previously would have been offered bypass surgery are now receiving DES. The debate of which is better (bypass surgery or stenting) in patients with complex coronary disease (multivessel CAD, total occlusions, left main CAD, etc.) continues.

The SYNTAX trial has compared the use of DES (paclitaxel-eluting) to CABG surgery in patients with over 1,800 patients with complex CAD who were randomized to either bypass surgery or multivessel stenting. The combined endpoint of death, repeat revascularization, stroke, and MI at 1 year favored bypass surgery. The differences were driven mainly by higher repeat revascularization rates in the stent arm of the trial. The risk of death or MI was no different in the two arms. The risk of stroke was more than three times higher in the surgical group. This trial, although providing some clear insights, has by no means put to rest the raging debate. The recommendation therefore is to individualize therapy after taking into considerations the following factors: (1) coronary anatomy, (2) LV function, (3) comorbid conditions, (4) age of the patient, and (5) patient's wishes.

**Intra-aortic Balloon Pump**

An IABP may occasionally prove needed for hemodynamic stabilization while awaiting PTCA or CABG, particularly for patients with LV dysfunction, CHF, hypotension, or acute mechanical defects (e.g., mitral regurgitation [MR] or ventricular septal defect [VSD]). Balloon inflation during diastole augments coronary perfusion and deflation during systole decreases LV afterload. Unless a rapidly correctable mechanical defect is present, IABP does not improve outcomes.

**Risk Factor Modification**

For the patient who has been stabilized medically or following revascularization procedures, risk factor modification is essential in preventing recurrent ischemia, infarction, and sudden death from progression of CAD.
Smoking cessation, control of diabetes mellitus and hypertension, correction of abnormal lipid patterns, and weight reduction are critical elements in risk factor modification. Most should remain on aspirin, β-blockers, high-dose statins, and angiotensin-converting enzyme inhibitors (ACEI). Establishing a regular program of exercise is pivotal in achieving these goals and improving activity tolerance. Patients with good exercise capacity are known to have fewer cardiovascular events and seem to tolerate them better.

**ACUTE CORONARY SYNDROMES: ST ELEVATION MYOCARDIAL INFARCTION (ACS-STEMI)**

**Mechanisms**

STEMI results from plaque rupture and formation of superimposed thrombus. The thrombus that causes complete occlusion of a major coronary artery is usually rich in fibrin and red blood cells (red clot). This is in contrast to the thrombus seen with NSTEMI, which is characterized by formation of a platelet-rich thrombus (white clot). Following complete coronary occlusion, a wave of myocardial necrosis spreads from the endocardium to the epicardium. The process of infarction is usually completed in 24 hours, and it is called a “full-thickness” or completed infarction. Q waves are typically seen in the ECG with a completed or full-thickness infarction, but their presence does not always indicate a finalized pathogenic process. If angiography is performed promptly, a fresh occlusive coronary thrombus may be demonstrated in most cases (approx. 90%).

Nonthrombotic spasm of the coronary arteries in an area of atherosclerosis is responsible for a small fraction of AMIs. Rarely, coronary flow may be interrupted by embolism in patients with endocarditis, prosthetic valves, or rheumatic valvular disease. Only 5% to 10% of patients sustaining an MI have anatomically normal coronary arteries. (Although spontaneous thrombolysis of clot is suspected, the mechanism of infarction in these cases usually remains unknown.) Cocaine is responsible for an alarming number of MIs. Because cocaine enhances platelet aggregation, causes vasoconstriction, and increases heart rate through catecholamine-mediated mechanisms, it can produce infarction even in patients with normal coronary arteries.

### Diagnosis

**History**

1. **Classical Presentation:** The typical presentation is one characterized by the abrupt onset of left-sided or retrosternal chest, neck, and jaw discomfort, which has been described as burning, squeezing, or pressure-like sensation lasting for more than 30 minutes. The discomfort may radiate to the arms, neck, back, or jaw. It must be emphasized that the pain description may be highly atypical (burning, stabbing, sharp) or may be localized only to the arm, neck, or epigastrium. Autonomic symptoms (nausea, vomiting, sweating) are more common than in UA, especially when the MI is inferior. Up to 20% of MIs are painless (more likely in diabetics and the elderly). Young age, paucity of classic risk factors, and atypical chest pain character are more common in patients with cocaine-induced infarction.

2. **Atypical Presentation:** Symptoms may mimic gastroesophageal reflux, cholecystitis, or an acute abdomen. Acute onset of shortness of breath, heart failure, dizziness, syncope, and weakness are occasionally encountered as atypical manifestations of an AMI.

3. **Silent MI:** Clinically silent infarcts are detected incidentally on an ECG, echocardiogram, or nuclear scan. Silent MI is usually experienced by diabetics with autonomic dysfunction.

### Physical Examination

Blood pressure and pulse rate usually are mildly increased. (Tachycardia is more common in anterior
or lateral MI than in inferior or posterior MIs, in which bradycardia is more likely.) Fever may accompany uncomplicated MI but rarely exceeds 101°F or persists beyond 1 week. An S4 gallop is very common, whereas an S3 suggests congestive failure, especially if accompanied by pulmonary rales. A paradoxically split S2 indicates increased LV ejection time or left bundle-branch block (LBBB). A systolic murmur should raise the suspicion of acute papillary muscle dysfunction, especially if the patient has presented late (typically, a few days after onset of symptoms). A pericardial friction rub commonly appears in the first 48 hours after a transmural MI and may be easily confused with a murmur. Although also possible in a classic MI, findings of a hyperadrenergic state (mydriasis, agitation, hypertension, diaphoresis, and/or tachycardia) should raise suspicion of cocaine-induced infarction.

**Electrocardiogram**

1. **ST Segment Deflection:** ST elevation greater than or equal to 1 mm in two or more contiguous leads is highly suggestive of STEMI. ST elevation has high localizing value (Table 21-1). The typical ST elevation seen with STEMI has an outward convexity. The ST segment elevations usually return to baseline with myocardial reperfusion and can be used to monitor reperfusion therapies. The differential diagnosis includes hyperkalemia, acute central nervous system (CNS) injury, acute myocarditis, acute pericarditis, left ventricular hypertrophy, apical cardiomyopathy, Wolff-Parkinson-White syndrome, early repolarization abnormalities, and LV aneurysm. Some of these may mimic an AMI and hence have been termed “pseudoinfarct” patterns.

2. **Evolution of ECG Changes:** A series of repolarization changes are seen on ECG after complete coronary artery occlusion. The first transient abnormalities seen are the hyperacute T waves (tall, peaked, and symmetrical T waves). Hyperacute T waves are usually gone by the time of initial presentation for emergency care. This is followed by convex, upward ST elevation, which is a sign of transmural myocardial ischemic injury. The number of leads showing the abnormality has a bearing on the size of the infarction and prognosis. T wave inversions are seen with persistent transmural ischemia. By this time, the ST elevations have begun to subside. Q waves are a sign of completion of the infarction and may take hours to days to develop. Persistent ST elevation beyond 3 to 4 weeks is a sign of an LV aneurysm.

3. **Posterior MI:** This manifests as ST depression (>2 mm) in leads V₁ to V₃. It is usually seen in conjunction with an inferior wall MI, but can present on its own as a true posterior infarction. This may occur with either left circumflex or distal RCA occlusion.

<table>
<thead>
<tr>
<th>Location of Injury</th>
<th>Affected Leads</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior</td>
<td>II, III, F</td>
</tr>
<tr>
<td>Anterior/septal</td>
<td>V₂-V₄</td>
</tr>
<tr>
<td>Anterolateral</td>
<td>V₃-V₆</td>
</tr>
<tr>
<td>Location</td>
<td>Leads</td>
</tr>
<tr>
<td>--------------</td>
<td>-------</td>
</tr>
<tr>
<td>Lateral</td>
<td>I, AVL, occasionally V₆</td>
</tr>
<tr>
<td>Apical</td>
<td>II, III, F, V₅, V₆</td>
</tr>
<tr>
<td>Posterior</td>
<td>V₁ and V₂ and V₃R, V₄R</td>
</tr>
</tbody>
</table>

aST segment depression with R waves; T wave is inverted initially and then becomes upright.

4. **RV Infarcts:** In about 30% of inferior wall infarctions, RV infarcts manifest on ECG as ST depressions in V₁ and V₂ and ≥1 mm ST elevations in right-sided chest leads, particularly V₃R and V₄R. Pure RV infarcts resulting from occlusion of RV marginal branch vessels may sometimes mimic an anterior MI by causing ST elevations in leads V₁ and V₂.

5. **New LBBB:** New LBBB is typically seen with large MIs and carries an in-hospital mortality rate of 20% to 25%. There is a substantial benefit from reperfusion therapy (21% reduction in mortality at 7 weeks, which translates into 49 lives saved per 1,000 patients treated). However, an MI may be missed in a significant number of individuals with new complete LBBB, and therefore, they are less likely to get reperfusion therapies than STEMI patients. Criteria for diagnosis of MI in the presence of LBBB are based on ST segment concordance or discordance: (1) greater than or equal to 1 mm concordant elevation, (2) greater than or equal to 5 mm discordant elevation, and (3) greater than 1 mm ST segment depressions in leads V₁ to V₃. Presence of one or more of these criteria makes a diagnosis of AMI more likely with LBBB.

6. **Normal ECG:** ECG may be normal in high lateral wall infarctions, as this area may be electrocardiographically “silent.”

**Cardiac Enzymes**

**Creatine Kinase**

Although now of secondary prominence to troponins, traditional creatine kinase measurements continue to be diagnostically helpful. Total CK and MB fractions begin to rise by 4 to 8 hours of onset of an MI, reach a peak by 18 to 24 hours, and return back to baseline by 48 to 72 hours. CK peaks earlier in non-Q wave infarctions and in patients who have received thrombolytic therapy to abort an acute infarction. The rapid washout of CK associated with thrombolysis may produce peak enzyme levels as early as 30 minutes after reperfusion. Peak CK activity correlates with the extent of muscle loss.

Levels are checked every 8 hours, and three negative CK-MB levels help rule out an AMI. CK-MB levels greater than 3% of total CK levels are used to make a diagnosis of an AMI. The sensitivity and specificity of CK-MB in the diagnosis of an AMI are lower than that of troponin. Thus, one may have a small infarct with normal CK-MB but slightly elevated troponins. Total CK may be mildly elevated by trivial skeletal muscle injury (e.g., severe exercise or intramuscular injection). Even though CK-MB is relatively specific for cardiac muscle, it may be released during massive skeletal or smooth muscle damage (e.g., rhabdomyolysis, polymyositis, small bowel surgery).

**Cardiac Troponins**

There are two types of cardiac troponin assays available (T and I). Both are cardiac-specific regulatory proteins; troponin-I is in more widespread use. Highly sensitive and specific in making a diagnosis of AMI, their levels elevate within 6 to 8 hours of onset of an AMI, peak by 3 to 5 days, and generally last for 7 to 12
days. Renal insufficiency slows their clearance. Thus, they aid in making a diagnosis of a remote MI. They are also helpful in making a diagnosis of an MI in certain situations like rhabdomyolysis, polymyositis, and renal failure where the CK-MB levels may be elevated.

Although sensitive, the serum aspartate aminotransferase is not sufficiently specific for diagnosis. Similarly, total lactic dehydrogenase (LDH) rises in most cases of MI but has a low specificity. Levels of the LDH-2 isoenzyme normally exceed those of the LDH-1 isoenzyme. Reversal of the ratio suggests MI. LDH begins to rise 12 to 24 hours after coronary occlusion, peaking at 2 to 4 days and resolving in 7 to 10 days. Because LDH rises later than creatine phosphokinase (CPK), it may be used to diagnose infarction in patients presenting more than 24 hours after onset of symptoms. Accumulating experience with troponin-I suggests it to be a sensitive and specific serum marker of myocardial damage.

**Echocardiography**

Although echocardiography cannot be considered a definitive test for ischemia, it is a helpful adjunctive technique. Echocardiography offers information that can help make a diagnosis of ischemia or infarction. A focal wall motion abnormality seen on the echocardiogram in the proper clinical setting can help make the diagnosis of acute ischemia or infarction, especially when the ECG is not helpful. Echocardiography can also help in providing an explanation for hypotension or congestive symptoms in patients with an AMI (e.g., LV or RV dysfunction, pericardial effusion, free wall or septal perforations, acute mitral insufficiency, or aortic dissection). Apart from its value in risk stratification, echo is also instrumental in diagnosing complications of infarction (e.g., chordal disruption, papillary muscle dysfunction, septal perforation, pericardial effusion, free wall rupture, ventricular aneurysm, mural thrombus). The addition of transesophageal echocardiography to the diagnostic armamentarium has substantially increased the ability to detect subtle MR, small ventriculoseptal defects (VSDs), papillary muscle damage, and posterior wall infarction (see Chapter 2).

**Treatment**

During the last four decades, advances in coronary care—aggressive treatment of coronary ischemia and arrhythmias—have reduced the mortality of AMI from 30% to less than 10%. In part, this relates to timeliness of intervention and rapid triage to facilities in which definitive care can be provided (Fig. 21-4). Recently, the major therapeutic goal has been to limit infarct size, primarily by achieving early reperfusion. Reperfusion is achieved by pharmacologic or mechanical means and is performed in conjunction with measures to minimize myocardial oxygen demand. The early therapy of AMI has now evolved to a five-armed attack: (1) relieve pain and anxiety; (2) achieve reperfusion using thrombolytic therapy or PTCA in appropriate candidates; (3) improve the balance between myocardial oxygen supply and demand by using supplemental oxygen, nitrates, and β-blockers; (4) initiate antithrombotic therapy (aspirin and heparin) to prevent reformation of a second occlusive thrombus; and (5) limit infarct expansion, prevent adverse ventricular remodeling, and improve ventricular function. These initial steps are followed by critically important secondary prevention efforts, which include early use of aspirin, high-dose statins and clopidogrel; appropriate and cautious use of beta-blockers and ACE inhibitors; and subsequent modification of cardiac risk factors (Fig. 21-5).
FIGURE 21-4. Triage and reperfusion sequence for acute myocardial infarction with ST segment elevation (STEMI).
FIGURE 21-5. Management of patients with chest pain presentation algorithm.

**Initial Steps**

Patients with a chest pain history suggestive of AMI should be placed at bed rest, undergo immediate ECG testing, receive sufficient oxygen to assure normal arterial saturation while avoiding hyperoxia, and have two peripheral intravenous catheters inserted, at which time blood samples should be drawn for electrolyte, hemoglobin, and CPK and troponin analyses.

Whenever possible, central venous catheters and arterial punctures should be avoided during antithrombolytic therapy. If the ECG is suggestive and the history is compatible with MI, aspirin and nitrates (if tolerated) should be administered to almost all patients while the intervention strategy is actuated. Opiates (classically morphine) and/or benzodiazepines should be considered for control of pain and anxiety. Unless contraindications exist, β-blockers should be administered to most patients with rapid tachycardia, but their use should otherwise be deferred until cardiac performance is assessed and stability is assured.

**Aspirin**
Because it is safe, fast, and effective at preventing recurrent thrombosis, aspirin (160 to 325 mg) should be given promptly to all patients with AMI without contraindications (e.g., history of aspirin allergy) and should be continued on a daily basis. Aspirin alone achieves an average 20% reduction in mortality, and when combined with other antiplatelet agents, an amazing 40% reduction in death rate is observed. For patients who are allergic to aspirin, clopidogrel used alone is less desirable but effective fall back option. Regardless of the suitability of the patient for thrombolytic therapy or angioplasty, an aspirin tablet once or twice daily reduces mortality risk and reinfarction rates for essentially all subgroups of patients with MI. Aspirin can be continued safely for years while providing continued benefit. Aspirin alone is as effective as preparations that combine it with sulfisoxazole or dipyridamole.

**Nitrates**

Unless contraindicated, NTG should be tried in nearly every patient having acute ischemic symptoms and an ECG suggesting MI. If a portion of the affected coronary artery remains patent, nitrates can promote flow through the narrowed segment. If the coronary occlusion is complete, however, nitrate therapy is unlikely to offer much, if any, boost in flow. Nitrates improve myocardial oxygen supply by reducing preload (and to a limited extent afterload) as well as by directly dilating coronary arteries. Intravenous nitrates may reduce infarct size and probably reduce mortality of AMI substantially. Except for hypotension or profound tachycardia, few contraindications to nitrate therapy exist. Nitrates should be used cautiously in inferior MI because of the potential to aggravate bradycardia and with great caution for patients with coexisting RV infarction, in whom small reductions in venous return can produce profound hypotension. Initially, sublingual or intranasal dosing makes sense because it is fast, is titrated easily, and can help alleviate symptoms while definitive reperfusion therapy is executed. If pain relief is achieved temporarily with sublingual or intranasal NTG, administration by continuous intravenous infusion often proves useful for longer relief. Long-acting oral nitrates should be avoided because of the inability to easily reverse or titrate their effects. Headache is common but easily treated with acetaminophen. Alcohol intoxication (from the intravenous vehicle) and methemoglobinemia are uncommon complications of prolonged intravenous infusion therapy.

**Analgesia and Anxiolysis**

Relief of pain and anxiety is important in the treatment of AMI. Ideally, ischemic pain is reversed by achieving reperfusion of the hypoxic cardiac muscle; however, direct analgesia may be necessary. Morphine, given in carefully measured doses, is the drug of choice. In addition to providing direct pain relief, morphine serves to reduce preload and, to a lesser degree, afterload—both potentially improving the balance in myocardial oxygen supply/demand. Furthermore, morphine inhibits anxiety-induced catecholamine release, further reducing myocardial oxygen consumption. Despite the fears of physicians, morphine-induced bradycardia and hypotension occur rarely; when they do occur, they usually respond promptly to fluids and/or low-dose atropine. Nausea is a more frequent problem that may warrant an opiate alternative such as carefully administered fentanyl. When analgesic range doses of morphine (2 to 10 mg) are given slowly, the risk of respiratory depression or any other complication is minimized. For the extremely anxious patient, especially one experiencing MI from cocaine use, benzodiazepines are very useful anxiolytic agents.

**β-Blockade**

Intravenous β-blockade given soon after the onset of MI may reduce infarct size and lower the risks of cardiac arrest, reinfarction, and death. These benefits are achieved predominantly by lowering myocardial oxygen consumption through reductions in heart rate, blood pressure, and contractility; however, β-blockers also provide independent antiarrhythmic effects. In addition to the early protective effects, continued therapy also lowers the long-term...
risk of symptomatic coronary disease for as long as 1 to 2 years. β-Blockers present significant risk for patients with seriously impaired left ventricular function and tendencies for congestive failure and shock and should not be used until hemodynamic stability is achieved. Nonetheless, given its proven benefits, it is curious that so few patients with MI uncomplicated by overt systolic dysfunction receive β-blocker therapy. Possibly, concerns over the potential side effects of therapy or lack of enthusiasm over a “low-tech” treatment are responsible.

Metoprolol and carvedilol are frequently selected as oral agents. (Suggested dosing regimens are listed in Table 21-2.) Absolute contraindications to β-blockade include known drug hypersensitivity, severe active bronchospasm, type I or type II second-degree atrioventricular (AV) block, complete heart block, sinus bradycardia (pulse <60), hypotension (systolic blood pressure <100 mm Hg), or overt LV failure (i.e., cardiogenic shock or pulmonary edema). Relative contraindications include insulin-dependent diabetes, concurrent use of a calcium channel antagonist, a history of obstructive lung disease, bibasilar rales, heart rates approximating 60 beats/min, systolic blood pressure near 100 mm Hg, and evidence for pulmonary venous hypertension (e.g., a wedge pressure higher than 20 mm Hg). If the blood pressure is marginal or if the history or physical examination suggests that the patient is prone to complications of β-blocker therapy, a short-acting intravenous agent such as esmolol (0.5 mg/kg load followed by 0.05 mg/kg/min infusion) can be tried and terminated rapidly should adverse response occur.

### Table 21-2. β-Blocker Regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>IV Load</th>
<th>Oral Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>5 mg repeated once after 10 minutes if pulse &gt;60</td>
<td>50 mg b.i.d or 100 mg daily</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>5 mg every 5 minutes, to a total dose of 15 mg</td>
<td>50-100 mg b.i.d</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>2.5 mg</td>
<td>12.5-25 mg b.i.d</td>
</tr>
<tr>
<td>Propranolol</td>
<td>0.1 mg/kg up to three times at 15-minutes intervals (hold for pulse &lt;50-60)</td>
<td>10-80 mg p.o. every 6 hours</td>
</tr>
</tbody>
</table>

**Insulin Infusion**

Hyperglycemia is quite common in patients with complicated AMI, as is the case with most acutely ill intensive care unit (ICU) patients. Influential trials have suggested that such patients benefit from aggressive control of blood glucose levels by insulin infusion. Although the wisdom of doing so is debated,
current recommendations are to start all STEMI patients with a complicated course and those who exhibit sustained hyperglycemia on an insulin infusion, targeting blood sugars 100 to 140 mg/dL.

**Magnesium Infusion**

Clinical trials have not demonstrated benefit from routine infusion of magnesium in STEMI patients. However, hypomagnesemia occurs in 30% to 40% of patients with AMI and should be corrected with intravenous and/or enteral therapies. The level is kept greater than 2 mmol/L to minimize risk of polymorphic ventricular tachycardia (VT) and ventricular fibrillation (VF).

**Reperfusion Therapies (Fig. 21-6)**

**Fibrinolytic Therapy**

**MECHANISM OF ACTION AND CHOICE OF AGENT**

Eighty-five to ninety percent of patients who sustain an AMI have coronary thrombosis. Fibrinolytics have been shown to limit infarct size, improve LV function, and reduce the mortality of certain patients with AMI by dissolving an intracoronary clot and restoring myocardial blood flow. The thrombolytic agents available for clinical use are (1) streptokinase (SK), (2) tissue plasminogen activator (t-PA or alteplase), (3) recombinant plasminogen activator (r-PA or Retavase), and (4) TNK-tPA (tenecteplase). All four agents accelerate conversion of plasminogen to plasmin, an enzyme that attacks fibrin and breaks down fibrin-rich or red clot. SK binds to plasminogen to form an activator complex. TNK-tPA and t-PA are fibrin-specific agents that act on clot-bound plasminogen and, therefore, do not cause a systemic “lytic” state. SK and to some extent r-PA cause a systemic lytic state. This systemic action usually produces a hypercoagulable state by reducing circulating levels of fibrinogen and most clotting proteins, like factors V and VIII, and increasing levels of fibrin degradation products. Unfortunately, none of these drugs can distinguish a “good” from a “bad” clot; therefore, all are associated with some increased risk of hemorrhage. The risk of bleeding is probably highest with r-PA and lowest with SK. Of all the available agents, the fibrin-specific agents are most effective in achieving a patent infarct-related vessel (80% with fibrin-specific agents compared to 50% to 60% with SK). Unfortunately, the accelerated t-PA regimen followed by an intravenous heparin infusion is associated with higher risk of major bleeding (including IC hemorrhage) than is SK. The rates of achieving a patent vessel are similar among t-PA, r-PA, and TNK-tPA. The bleeding risk is lower with TNK-tPA, as compared to the other fibrin-specific agents. TNK-tPA and r-PA are administered as bolus doses and are, therefore, much easier to administer compared to accelerated t-PA regimen. Therefore, the agent of choice (in the United States) is TNK-tPA, but SK continues to be popular in Europe and Asia, mainly because of lower costs. SK may also be preferable in older patients (>75 years of age), particularly for small-sized women, if PCI is not available.
FIGURE 21-6. ST elevation MI (STEMI) management algorithm. ACEI, angiotensin-converting enzyme inhibitor; NTG, nitroglycerin; PCI, percutaneous coronary intervention.

PATIENT SELECTION AND IMPORTANT FACTS REGARDING FIBRINOLYTIC THERAPY

- See Tables 21-3 and 21-4 for indications and contraindications of fibrinolytic therapy.

### Table 21-3. Indications for Thrombolytic Therapy

**ANGINOID CHEST PAIN OF LESS THAN 12-HOURS DURATION**

PLUS one or more of these:
- ST elevation ≥1 mm in at least two contiguous LIMB leads
- ST elevation ≥2 mm in at least two contiguous CHEST leads
- New LBBB

LBBB, left bundle-branch block.
Table 21-4. Contraindications to Thrombolytic Therapy

**ABSOLUTE CONTRAINDICATIONS**

- Active internal bleeding
- History of CNS disease (stroke, arteriovenous malformation, surgery, tumor, or head trauma) within 6 months
- Hemorrhagic CVA anytime in the past
- Suspected aortic dissection
- Underlying coagulopathy, including thrombocytopenia
- Ongoing warfarin therapy with INR > 2.5
- Severe diastolic hypertension (diastolic blood pressure >110 mm Hg)
- Recent (2-4 weeks) trauma, deep tissue biopsy, or operation
- Pregnancy

**RELATIVE CONTRAINDICATIONS**

- Systolic blood pressure >180 mm Hg
- Remote history of stroke or transient ischemic attack
- Recent prolonged (>10 minutes) cardiopulmonary resuscitation
- Needle puncture of a noncompressible vessel
- Intracardiac thrombus

CNS, central nervous system.

- All STEMI patient subgroups (age, gender, comorbid conditions) and infarct locations seem to benefit from fibrinolytic therapy when PCI is not available or delayed. The prior administration of fibrinolytic does not preclude subsequent PCI.
- Proportionately, the greatest benefits are experienced by patients at greatest risk: those with larger and anterior infarctions, those with new LBBB, and those in CHF.
- The benefit with fibrinolytic therapy is *timedependent*. For every 1,000 patients treated with fibrinolytics (compared to placebo), 65 lives were saved if treated within first hour of onset of symptoms, 26 lives if treated within 1 to 3 hours of onset of symptoms, and 18 lives if treated within 6 to 12 hours of onset of symptoms.
- Fibrinolytic therapy should be given to STEMI patients without contraindications within 12 hours of the onset of chest pain and if the *estimated door-balloon time is greater than 90 minutes* (absence of immediate PCI availability). Patients seen within 12 to 24 hours of onset of chest pain and with ongoing chest pain and persistent ST elevations may also be considered for fibrinolytic therapy if PCI is unavailable, but the magnitude of benefit is significantly lower. Fibrinolytic should not be used in STEMI patients presenting greater than 24 hours of onset of symptoms. Fibrinolytic therapy should be given within 30 minutes of arrival in the emergency room (door-to-needle time of ≤30 minutes), once a decision for their use has been made. It is also recommended that patients receiving fibrinolytic therapy should be transferred to a facility with PCI availability as soon as possible. Such transfer has been shown to be generally safe.
- Antithrombotic therapy with fibrinolytic therapy: UFH is used with fibrin-specific agents (t-PA, TNK-tPA,
It is generally not recommended with SK. It is given in a bolus dose of 60 units/kg (4,000 units maximum), followed by an infusion of 12 units/kg/h (1,000 units/h maximum). The dose of the infusion should be adjusted to keep PTT 1.5 to 2.0 times the upper limit of normal. The infusion is usually continued for 48 hours postfibrinolytic therapy. Heparin infusion should be continued beyond 48 hours if patients are at high risk for venous or systemic thromboembolic events (large anterior MI, severe LV dysfunction, CHF, thrombi in the LV, AF). Patients must be started on warfarin, and the heparin should be discontinued only once INR is greater than 2.

- Gp2b/3a receptor antagonists can be used with half-dose r-PA or TNK-tPA in patients below 70 years of age. In older patients, this combination increases the risk of bleeding.

- The limitations of fibrinolytic therapy include the following: (1) 20% to 30% patients have contraindications for thrombolytic therapy; (2) 50% to 70% patients have successful reperfusion; (3) recurrent ischemia or reinfarction is seen in 15% to 30% patients who experienced successful reperfusion; and (4) 4% to 5% patients experience major bleeding, including 0.7% to 1.5% risk of intracerebral hemorrhage (which has a high fatality rate).

- Indicators of successful reperfusion: significant improvement or complete disappearance of chest pain along with greater than 50% resolution of ST segment elevation on ECG within 90 minutes of administration of fibrinolytic therapy. The greater the degree of improvement of ST segment change, the better the long-term outcome.

### COMPLICATIONS OF FIBRINOLYTICS

1. **Hemorrhage:** Four to five percent of patients experience major bleeding (usually GI) and about 0.5% to 1.5% experience an IC bleed. Factors that predict risk of major bleeding are advanced age (>70 years), female gender, low body weight, hypertension at presentation, bleeding diathesis, IC neoplasms, and previous stroke. Fibrin-specific agents are more prone to cause bleeding than SK. IC bleeds are heralded by mental obtundation, focal CNS deficits, and intense headaches. With onset of these symptoms, one must stop the fibrinolytic therapy, heparin, and all antiplatelet agents including aspirin. A stat CT scan of the head will help confirm the diagnosis. The treatment consists of packed red blood cell transfusions (if hematocrit drops below 25% and there is associated hypotension), cryoprecipitate infusion (approx. 10 units), and fresh frozen plasma infusion if there is continued bleeding (2 to 6 units). Intravenous protamine (25 to 50 mg after a small test dose) may be needed to reverse the effect of heparin. Platelet transfusions (6 to 12 units) may be needed for continued bleeding, especially if the patient has received abciximab, clopidogrel, and aspirin. Patients with thrombocytopenia (<100,000/mm$^3$) have an 8- to 10-fold risk of bleeding with fibrinolytic therapy.

2. **Anaphylaxis:** Encountered rarely, primarily with SK. Prompt recognition, stopping the drug, airway maintenance, intravenous epinephrine (1 to 5 cc of 1:10,000 solution), intravenous fluid boluses, intravenous hydrocortisone, and methylprednisone are the cornerstones of therapy. Less commonly, intravenous dopamine, phenylephrine, or norepinephrine infusion and inhaled albuterol aerosol may be necessary for persistent hypotension.

3. **Hypotension:** Occurs in 10% to 15% patients with SK. Slowing the infusion rate and giving intravenous fluids usually suffices, but occasionally the drug infusion may have to be stopped temporarily until the blood pressure improves.

4. **Reperfusion Arrhythmias:** The usual reperfusion arrhythmias seen with fibrinolytic therapy are runs of idioventricular rhythm (IVR) (rate 90 to 120 beats/min) and VT. These rhythm disturbances are usually transient and do not need treatment other than β-blocker therapy. VF can also occur occasionally with reperfusion and this usually responds promptly to defibrillation. With inferior wall MI from dominant RCA
occlusion, one may see transient, third-degree AV block with reperfusion.

5. Miscellaneous: Fever, skin rash, and rigors. All these are more common with SK. Skin rash necessitates stopping infusion and considering t-PA or PCI. Benadryl and hydrocortisone given by intravenous route seem to help.

**Primary Percutaneous Coronary Intervention (PCI—PTCA and Stenting)**

- Primary PCI of the infarct-causing vessel is today the preferred method of reperfusion in patients with STEMI. Mechanical reperfusion with PTCA and stenting has been shown to be superior to fibrinolytic therapy. When performed soon enough, PTCA achieves TIMI-3 flow in the infarct-related vessel in approximately 90%, compared to 50% to 60% TIMI-3 flow rates with the best fibrinolytic regimen.

- The improved rate of establishing infarct vessel patency with PCI has translated into better clinical outcomes, compared to fibrinolytic therapy. In meta-analyses of trials comparing primary PTCA to fibrinolytic therapy, there has been reported 30% to 50% reduction of death, reinfarctions, and stroke at 1 and 6 months. Improvement in rates of stroke and reinfarction is responsible for most of the benefit seen with PCI. PCI has been shown to save 21 more lives than fibrinolytic therapy for every 1,000 patients treated.

- Although “sooner the better” definitely applies, PCI in STEMI is not quite as time-dependent as fibrinolytic therapy. Primary PTCA reduced 30-day rates of major cardiac events (death, reinfarction, CVA) by 54% in patients presenting within 2 hours of onset of symptoms, 39% for those presenting within 2 to 4 hours of symptom onset, and 21% for those presenting after 4 hours. This is not the case with fibrinolytic therapy, where the benefit diminishes exponentially with each passing hour after onset of symptoms.

- The risk of intracerebral hemorrhage is about 0.1% with primary PCI, which therefore is particularly a good option for those beyond 70 years of age, in whom fibrinolytic therapy significantly increases the risk of bleeding. It is the only definitive treatment that can be offered in those with absolute contraindications to fibrinolysis.

- High-volume centers are those that perform greater than 200 to 300 PCI procedures per year. Data from the National Registry for MI (NRMI) show that there is a 37% reduction in death in STEMI patients treated with PCI at high-volume centers and little change in mortality when treated at low-volume centers. However, a 64% reduction in risk of CVA was seen with PCI at both low and high-volume centers. Therefore, primary PCI is the preferred mode of reperfusion for STEMI patients if access to a high-volume cardiac catheterization laboratory is available and if PCI can be performed in a timely fashion. The ideal door-to-balloon time should be less than 90 minutes.

- **On-site** fibrinolytic therapy versus transfer of patients for PCI: When patients with STEMI arrive at a hospital without a cardiac catheterization laboratory, the question arises as to whether these patients are better off with on-site fibrinolytic therapy or with transfer for PCI to a larger center with cardiac catheterization facilities. The DANAMI-2 and PRAGUE-2 trials have both shown benefit of transferring patients for primary PCI over on-site fibrinolytic therapy, if the transfer of patients can be achieved within 2 hours. In the DANAMI-2 trial, there was a 40% reduction in reinfarction, death, and CVA at 30 days, compared to fibrinolytic therapy. The transferred patients have outcomes with PCI comparable to those who present directly to the invasive treatment center. Transfer of patients was found to be safe, with very few adverse events during transportation. Thus, establishment of primary PCI centers with 24/7 cardiac cath-lab facilities and efficient patient transfer protocols is key to improving outcomes in patients with STEMI. The door-to-balloon time is approximately 3 hours in the United States for patients with STEMI transferred for PCI (time of entry to the first emergency room to the time of balloon inflation at the PCI). Therefore, the prevailing guidelines in the United States would favor the administration of fibrinolytic
therapy for lytic-eligible patients—if the door-to-balloon time is likely to exceed 90 minutes. These patients must be transported to a PCI center soon after administration of fibrinolytic therapy, so that if they fail to achieve reperfusion, then they could still undergo PCI and mechanical reperfusion in an expeditious manner. For patients with contraindications for fibrinolytics (lytic ineligible) and in situations where the door-to-balloon time is likely to be less than 90 minutes, quick transfer to another hospital for primary PCI is the best approach.

- **PTCA versus intracoronary stenting in AMI:** Stents improve long term outcome from PTCA. Meta-analysis of all the stent-versus-balloon angioplasty trials shows 46% reduction in composite endpoint of death, reinfarction, and target vessel revascularization at 6 months using stents compared to PTCA alone. This difference was mainly due to reduced restenosis and recurrent ischemia.

- **Drug-eluting versus bare-metal stents:** Baremetal stents have been in clinical practice in the United States since 1994. In 2003, the FDA approved sirolimus (Rapamune) and paclitaxel (Onxol, Taxol) DES for clinical use. Zotarolimus and everolimus-eluting stents have also been approved by the FDA. These stents are made of stainless steel and are covered with a polymer, which elutes an antiproliferative drug. The stents usually elute the drug for a period of 3 to 6 weeks from the time they are deployed in the artery. The main advantage of DES as compared with the older bare-metal stent is reduction of restenosis from excessive neointimal proliferation. Neointimal proliferation occurs as a result of intimomedial injury caused by the stent. The antiproliferative agent eluted by the stent prevents neointimal proliferation in the artery. These devices are now used extensively in patients with CAD, including in those with AMI. The use of DES has reduced clinical restenosis rates quite dramatically compared to those receiving baremetal stents (5% to 9% vs. 20% to 40%). DES has been shown to have superior clinical outcomes in all subsets of patients, including AMI. The major disadvantage of stents, particularly DES, is stent thrombosis, which can cause catastrophic MI or death. Patients who receive bare-metal stents should remain on dual antiplatelet therapy (e.g., clopidogrel and ASA) for a minimum of 1 month. The recommendation is for a minimum of 12 months of dual antiplatelet therapy for patients with DES. However, over the course of the last few years, it has become apparent that a small group of patients with DES will suffer from the phenomenon of **late stent thrombosis**, especially with discontinuation of clopidogrel therapy. That is the reason why most patients who receive DES remain on dual antiplatelet indefinitely.

- **Role of thrombus aspiration:** Thrombus aspiration with an aspiration catheter from the occluded vessel prior to balloon PTCA or stenting had been long felt to improve TIMI-3 flow, myocardial blushing, and myocardial salvage. Myocardial blushing on contrast angiography is perhaps a better indicator of clinical outcomes like resolution of ST elevation on ECG and myocardial salvage than angiographic TIMI flow rates. Myocardial blush grade 0 to 1, no or very little blush; 2, moderate blush; and 3, normal blush indicate no or minimal, moderately reduced, and normal myocardial perfusion, respectively. The TAPAS trial, which randomized more than 1,000 patients with STEMI, compared efficacy of standard practice of balloon angioplasty plus stenting to thrombus aspiration plus stenting, in terms of improvement in myocardial blushing. Thrombus aspiration followed by stenting was superior to standard practice of PTCA and stenting in improving myocardial perfusion. This is mainly because thrombus aspiration reduces the risk of the clot breaking loose to occlude the distal coronary microcirculation. Although the 30-day event rate (death and nonfatal MI) was statistically no different between the two groups, the 1-year follow-up data showed a clinical trend that favored thrombus aspiration.

- **Door-to-balloon (or device) times and prehospital cardiac cath-lab activation:** The standard recommendation for door-to-balloon time in STEMI patients is less than 90 minutes for both direct admits and for patients being transferred for PCI (door time = time of initial patient arrival in the ER; balloon or
device time = time of first balloon inflation or device use [like clot aspiration]). Some cardiac hospitals have developed protocols where the paramedics activate the cath lab from the field after performing a prehospital ECG. The patient is usually brought in directly to the cath lab bypassing the emergency room, thereby reducing delays. This system has helped reduce door-to-balloon times significantly at these institutions. However, there are times when patients with NSTEMI (and/or LVH, pericarditis, early repolarization, etc.) end up arriving in the cath lab inappropriately. The AMI protocol has also been refined significantly in many of the emergency rooms through joint collaboration between the emergency room physicians and the cardiologists. The usual rule is to get the first ECG within 10 minutes of first encountering a patient with chest pain. Having an AMI protocol streamlines care and reduces delays significantly. The on-call cath-lab team including the interventional cardiologist should be living within 15 to 20 minutes of the hospital. Most often, the patient gets a chest X-ray and, after an aortic dissection is ruled out, gets started on heparin and a Gp2b/3a receptor antagonist, before the cath-lab team takes the patient to the cath lab for PCI.

- **Facilitated PCI:** In small, nonrandomized single-institution studies, there appeared to be some benefit from use of half-dose preprocedural lytic therapy in patients being transferred for PCI. There were early reports of improved TIMI-3 flow with this strategy. However, a large randomized trial (FINESSE) looking into this matter failed to show any benefit with half-dose lytic therapy prior to angioplasty. Therefore, preprocedural lytics are no longer recommended.

- **Rescue PCI:** Patients who fail to achieve reperfusion with fibrinolytic therapy should be transferred to a hospital for emergent PCI. The results of rescue PCI have improved over the last decades with the increased use of intracoronary stents and Gp2b/3a receptor antagonists during PCI. Persistent ST elevation and chest pain 90 minutes after administration of fibrinolytic agent and hemodynamic instability therefore signal the wisdom of emergency angiography and rescue PCI.

- **Immediate or adjunctive PCI:** Coronary angiography and PCI that is performed routinely within hours or days after successful reperfusion with fibrinolytics are called immediate or adjunctive PCI. After successful fibrinolysis, there usually is a significant residual plaque in the infarctrelated vessel that potentially can cause recurrent ischemia or reinfarction. Multiple clinical trials support adjunctive PCI performed routinely after fibrinolytic therapy. There are, however, certain specific indications for postfibrinolytic cardiac catheterization and revascularization: (1) previous history of MI, CAD, PCI, or bypass surgery; (2) LV dysfunction with LVEF less than or equal to 40%; (3) recurrent ischemia (either spontaneous or by stress testing); (4) ventricular tachyarrhythmias with hemodynamic instability; and (5) VT after the first 48 hours of reperfusion.

- **Delayed PCI:** Delayed PCI several days after fibrinolysis is fully justified for recurrent ischemia, reinfarction, heart failure, or significant ventricular arrhythmias. With successful PCI, ventricular remodeling and LVEF are improved and these patients may tend to have fewer ventricular arrhythmias. Thus, it may be worthwhile attempting late revascularization (PCI or CABG surgery) in occluded coronary vessels if there is evidence of myocardial viability—especially if a large area of myocardium is in jeopardy.

- **Antithrombotic therapy in primary PCI:** Patients undergoing primary PCI for STEMI should receive UFH (50 to 70 units/kg bolus followed by an infusion at rate of 12 to 15 units/kg/h). Heparin should be started while the patient is waiting to be transferred to the cardiac catheterization laboratory. An infusion of heparin after the procedure is unnecessary, unless an IABP is used or if the result is unsatisfactory and there is ongoing ischemia postprocedure. The vascular sheaths are generally removed 3 to 6 hours after heparin dosing (typically when the ACT is below 170 seconds). Enoxaparin can be used as an
alternative to heparin in the dose of 1 mg/kg subcutaneously twice daily. There is no need to monitor ACT or for additional antithrombotic therapy if PCI is done within 8 hour of enoxaparin dose. The vascular sheaths can be removed 8 to 12 hours after the last dose of enoxaparin.

- **Bivalirudin in STEMI**: The influential HORIZONS-AMI trial showed lower cardiac death and bleeding rates at 30 days with bivalirudin (a DTI) compared to standard treatment of heparin combined with Gp2b/3a receptor antagonists in STEMI patients undergoing emergent PCI. The drug although has become popular among interventional cardiologists despite its relatively high cost.

- **Gp2b/3a receptor antagonists in primary PCI**: Gp2b/3a receptor antagonist agents have been routinely used in patients with AMI. Abciximab has been shown to be beneficial in STEMI patients and as a pharmacological adjunct for primary PCI, and many interventional cardiologists use this agent routinely in almost all STEMI patients. Given the efficacy of safer dual antiplatelet regimens, others prefer to use it selectively in those with large thrombus burden, diabetic patients, and complications like distal embolization and dissections. Many hospitals are now using one or the other smallmolecule agents (eptifibatide and tirofiban) for patients with STEMI, because the incidence of dangerous bleeding, thrombocytopenia, and pulmonary hemorrhage is lower with these agents as compared with abciximab. For best results, the medications should be started prior to the PCI procedure.

- **Clopidogrel**: This is given as a 300- to 600-mg bolus at the completion of the acute infarct PCI, particularly in those who receive intracoronary stents. The medication is generally continued for a minimum of 12 months in AMI patients receiving DES. The primacy of more potent and recently introduced alternatives (e.g., prasugrel and ticagrelor) has not yet been established.

**Indications for CABG in STEMI**

- Urgent or emergent CABG may be necessary in 5% to 8% of patients with STEMI undergoing emergent PCI. The usual indication for emergent CABG is failure of reperfusion with PCI, a large area of jeopardized myocardium, in a patient with coronary anatomy suitable for CABG. That emergent rescue approach is especially attractive if the patient is within 6 to 12 hours of an acute infarction.

- Patients with mechanical complications of an MI, such as acute MR, acute VSD, or wall ruptures, are also candidates for emergent surgery. Patients with certain coronary anatomies may benefit from emergent or urgent CABG: severe left main disease (>70% stenosis) and severe proximal multivessel disease (especially those with CHF or cardiogenic shock).

- Mortality is 10% to 15% in STEMI patients undergoing emergent CABG within the first few hours of infarction. However, this may be the only way to salvage myocardium in some patients with STEMI who fail PCI. Improvement in techniques for myocardial preservation (like use of blood cardioplegia) during CABG has certainly improved outcomes with emergent surgery. Also, it is important to keep bypass pump time short in these patients. In fairly stable patients, one should try to graft the LIMA to the LAD artery (wherever applicable), but in unstable patients, vein grafts are preferred, as this shortens the time on the bypass pump.

- In patients with cardiogenic shock who are less than 75 years of age, emergent bypass surgery should be considered as soon as possible if they are not candidates for PCI or if they fail PCI. Stabilization with IABP counterpulsation and vasopressors is necessary before and after surgery in most of these patients. In patients with STEMI presenting late (>12 to 24 hours) and in the need for CABG, it may be advisable to wait for a few days to a week before surgery, especially if they are not showing any signs of acute ischemia and are relatively stable hemodynamically. The surgical mortality in stabilized STEMI patients is lower than in those who undergo emergent surgery within the first 24 hours of infarction.
In patients needing emergent CABG, use of Gp2b/3a receptor antagonist and clopidogrel before surgery will increase risk of bleeding. These agents must be stopped as soon as the decision to operate on these patients is made. Cautious dosing of heparin based on ACT while going on bypass pump may also reduce the risk of bleeding in these patients, many of whom would have also received Gp2b/3a receptor antagonists. For patients who have received abciximab and/or clopidogrel, infusion of 6 to 12 units of platelets while coming off pump will serve to reduce postoperative bleeding.

Medical Treatment after Reperfusion Therapy

1. **Antiplatelet Therapy:** Aspirin (81 to 162 mg/d) should be given indefinitely to all patients with history of MI or CAD. Clopidogrel is routinely given for all those who receive stents for a duration of 6 to 12 months or longer.

2. **Angiotensin-Converting Enzyme Inhibitors:** ACEIs favorably influence ventricular remodeling after AMI, thereby reducing the risk of dilated cardiomyopathy, CHF, and death. The benefits of ACEI therapy in post-MI patients have been shown in several large trials, including GISSI-3 and ISIS-4. The greatest benefits have been observed in patients at highest risk (e.g., patients with large anterior wall infarctions, patients who are older than 70 years of age, and women). Ideally, an oral ACEI is started within 48 hours of the onset of the infarction in those who have been stabilized. Intravenous dosing and use of “loading doses” are not only unnecessary but may prove harmful. Several examples of potential ACEI regimens are presented in Table 21-5. Contraindications to ACE therapy include known hypersensitivity, cardiogenic shock, renal failure, and bilateral renal artery stenosis. Renal insufficiency is not a contraindication for ACEI therapy, but one should monitor creatinine and potassium closely. In patients at low risk, there may not be any benefit beyond the first 3 to 6 months of an AMI. By contrast, high-risk patients (such as those with ejection fraction below 40%, overt heart failure, or clinical evidence of a large infarction) benefit from long-term (potentially permanent) therapy. As a matter of practicality, virtually all tolerant patients with MI started on an ACEI continue the medication indefinitely. Large trials have failed to substantiate fears that ACEI could worsen outcome by precipitating hypotension.

**Table 21-5. ACEI Regimens**

<table>
<thead>
<tr>
<th>Captopril</th>
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<tbody>
<tr>
<td>6.25 mg p.o., followed 2 hours later by 12.5 mg p.o., followed 12 hours later by 25 mg p.o., then 50 mg p.o. b.i.d</td>
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<table>
<thead>
<tr>
<th>Lisinopril</th>
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<tr>
<td>5 mg p.o. daily for 2 days, then 10 mg p.o. daily</td>
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<table>
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<tr>
<th>Enalapril</th>
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<tr>
<td>2.5 mg p.o. b.i.d. titrated upward to 10 mg p.o. b.i.d. as tolerated</td>
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</table>
3. **Angiotensin II Receptor Blocker Antagonists** (e.g., alsartan or candesartan) often can be used instead of ACEI in post-AMI patients who are intolerant to ACEI and have LVEF less than 40% and/or CHF.

4. **β-Blockers:** When well tolerated, β-blockers reduce risk of recurrent MI and sudden death in patients with previous MI. They also may help prevent adverse LV remodeling after an MI (along with ACEI therapy) and risk of ventricular arrhythmias. Long-term β-blocker therapy, typically with either metoprolol or atenolol (β₁ receptor antagonists), is recommended. Carvedilol is considered preferable for patients with severe LV dysfunction and heart failure. In this patient population, this agent has been shown to significantly reduce mortality. Far more expensive than metoprolol or atenolol, carvedilol blocks β₁-, β₂-, and α-receptors and has also been shown to have antioxidant properties. β-Blockers have been shown to improve survival in all patient subgroups, including those in whom they are traditionally considered as relatively contraindicated (diabetics, chronic obstructive pulmonary disease [COPD], heart failure, and peripheral vascular disease). Just as with ACEI therapy, β-blockers should be started in small dosage and gradually increased as tolerated. They must be used with caution in those with severe COPD or bronchospasm, overt CHF, bradyarrhythmias, and brittle diabetes.

5. **Aldosterone Antagonists:** Eplerenone (an aldosterone receptor antagonist) was reported to reduce mortality in post-MI patients with severe LV systolic dysfunction already taking ACEI and β-blockers in the EPHESUS trial. Spironolactone is another agent with similar action that could potentially be used in these patients. Although cheaper in cost, spironolactone has more unpleasant endocrine side effects compared to eplerenone. These include hirsutism in women and painful gynecomastia in men. Therefore, all post-MI patients with LVEF less than 40%, symptomatic CHF, or diabetes mellitus and without renal failure (creatinine <2.5 mg%) or hyperkalemia (potassium >5.0 mmol/L) should be considered for an aldosterone antagonist if they are already on an ACEI. Creatinine and potassium must be monitored closely in all patients receiving an aldosterone antagonist.

6. **Statin and Alternative Cholesterol Management:** Multiple, secondary prevention trials have all shown reduction of reinfarction and death in post-MI patients receiving high-dose statins. Lowering LDL cholesterol level is the primary goal; however, it can be reached. Benefit may accrue even in those with LDL-c less than 100 mg/dL. Current guidelines suggest achieving a goal LDL-c level less than 70 mg/dL in these patients, with use of powerful statin drugs like atorvastatin or rosuvastatin. One must monitor these patients periodically for side effects like myalgias, myositis, and drug-induced hepatitis. Statin therapy should be continued indefinitely if well tolerated. If the patient experiences side effects, lower doses or a switch to a less powerful statin like pravastatin seems indicated. Failure to reach LDL targets despite dietary and lifestyle changes and tolerated doses of statin should prompt consideration of adding other classes of drug such as the fibrates and dietary cholesterol blockers (e.g., ezetimibe [Zetia] or bile salt sequestrants). The dramatic LDL-lowering potency (and extraordinarily high cost) of recently introduced human monoclonal antibody agents (alirocumab [Praluent] and evolocumab [Repatha]) suggests that a new era of cholesterol management may be dawning.

7. **Antiarrhythmic Agents:** Routine use of prophylactic antiarrhythmic therapy is not necessary in patients with AMI. Even though PVCs and nonsustained VT are markers of increased risk of SCD, especially in
the setting of decreased LV systolic function, their suppression with antiarrhythmic agents may actually result in increased mortality because of their proarrhythmic potential (CAST trial findings). The best way to reduce risk of SCD in these patients is by means of quick reperfusion, and judicious use of β-blockers and ACEI, as already discussed. β-Blockers and ACEI have been shown to reduce SCD over the long term through positive ventricular remodeling, which also ensures electrical stability. Antiplatelet agents (aspirin, clopidogrel) and statins have also been shown to reduce SCD long term in post-MI patients. There is epidemiological evidence supporting the use of fish oils rich in omega-3 fatty acids, which have been shown to reduce the risk of SCD. In patients with STEMI resuscitated from VF arrest and in those with symptomatic sustained VT, one may consider amiodarone, which is not only very effective in suppressing ventricular and supraventricular arrhythmias but also one of the safest antiarrhythmic agents from the standpoint of proarrhythmia. It may also be indicated for prophylaxis against recurrent AF, in which case it is usually given for 8 to 12 weeks. In dire emergencies like resuscitated VF arrest, sustained VT, and symptomatic supraventricular tachycardia (SVT) including AF, it is usually given intravenously in the dose of 150 mg bolus followed by infusion of 1 mg/min for 6 hours, followed by infusion of 0.5 mg/min for 18 hours. This is usually followed by oral amiodarone therapy lasting for 3 to 6 months or longer.

8. **Calcium Channel Blockers:** Although they are effective for controlling acute hypertension, reversing coronary spasm, and relieving pain of coronary thrombosis, calcium channel antagonists have not improved survival in several clinical trials; in at least one study, shortacting nifedipine adversely affected survival. Therefore, the routine use of calcium channel antagonists cannot be advocated. In the event of severe hypertension complicating AMI or UA, however, diltiazem or amlodipine may be used along with the use of ACEI agents and β-blockers.

9. **Oral Anticoagulants:** Chronic systemic anticoagulation is indicated in those at risk for systemic or venous thromboembolism, like those with large anterior MI with akinetic apex, severely reduced LV function, AF, and presence of LV thrombus on echocardiography (see Chapter 30). In patients with large anterior MI, oral anticoagulants (warfarin or newer alternatives) may be continued for 3 to 6 months.

**General Support of the ACS Patient**

Close monitoring for electrical and mechanical complications and direct control of pain and stress are basic measures applied to all MI victims. A liquid diet usually is provided for 24 hours after infarction. Temperature extremes of foods are avoided in an attempt to minimize the risk of arrhythmias. Sedation and stool softeners to prevent anxiety and straining also may decrease the risk of arrhythmias. When systemic anticoagulation is not performed, subcutaneous heparin (7,500 units SQ b.i.d.) or enoxaparin (40 mg SQ, once daily) is indicated for the prevention of deep venous thrombosis for patients with MI on strict bed rest. Bed rest is mandatory during the initial day of management. However, once adequate reperfusion and stability are assured, early ambulation is advisable. Cardiac rehabilitation personnel should make an initial evaluation, preferably soon after reperfusion therapies. Despite numerous large-scale clinical trials, several commonly used therapies remain of unproven benefit (Tables 21-6 and 21-7).

**Outcome of Myocardial Infarction**

Overall, MI carries a mortality risk of approximately 15% to 20%. Most deaths occur within the first hour or two of infarction and are the result of prehospital ventricular arrhythmias, which, to a large degree, cannot be prevented. The in-hospital death rate is around 5% to 9%, which has improved significantly over the last 4
decades, because of advances in reperfusion therapies. In contrast to prehospital mortality, most deaths in
patients reaching the hospital occur from refractory pump failure. Therefore, survival is maximized by limiting
infarct size and by promptly treating mechanical and electrical complications. Survival is best predicted by the
patient's age, preinfarction physical fitness, degree of left ventricular impairment (a reflection of the mass of lost
myocardium), and comorbid conditions.

Table 21-6. Unproven Interventions in Acute MI

- Antiarrhythmic agents
- Calcium channel antagonists
- Magnesium sulfate therapy

Table 21-7. Therapy of Acute MI

<table>
<thead>
<tr>
<th>ACUTE THERAPY</th>
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<tbody>
<tr>
<td>Aspirin, 325 mg p.o.</td>
</tr>
<tr>
<td>Sublingual TNG p.r.n. for pain</td>
</tr>
<tr>
<td>Morphine sulfate, 2-10 mg IV p.r.n. for pain</td>
</tr>
<tr>
<td>Oxygen 2-3 L by nasal cannula</td>
</tr>
<tr>
<td>IV β-blocker</td>
</tr>
<tr>
<td>Consider thrombolytic therapy, PTCA</td>
</tr>
<tr>
<td>Continue ECG monitoring, daily aspirin, and β-blocker</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DAY 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral ACEI for high-risk patients</td>
</tr>
<tr>
<td>Begin risk factor modification</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DURING HOSPITALIZATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider starting ACEI and β-blocker if not started on admission</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6 WEEKS POST-DISCHARGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue ACEI for low-risk patients with ejection fraction &gt;40%, without CHF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1-YEAR POST-DISCHARGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue β-blocker if low risk and no other indications exist for its use</td>
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<table>
<thead>
<tr>
<th>INDEFINITELY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue aspirin and risk factor modification</td>
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</table>
COMPLICATIONS OF MYOCARDIAL INFARCTION

Half of all patients sustaining MI have no significant complications. Of those with a complicated course, most serious events occur within the first 5 days. Complications generally fall into one of two categories—electrical or mechanical. Because specialized coronary care units are able to immediately detect and treat arrhythmias, mechanical complications have assumed relatively greater importance.

Electrical Complications

A detailed discussion of arrhythmias, heart block, and the use of cardiac pacing is presented in Chapter 4. Tachyarrhythmias occur very commonly within the first 3 days after MI as a result of the electrical instability caused by ischemic or dying cells. Fortunately, most early tachyarrhythmias are self-limited. These early arrhythmias have little prognostic import if they receive appropriate treatment when symptomatic. A major change in the philosophy of caring for patients with MI has occurred in the practice of tachyarrhythmia treatment. Whereas essentially all patients with MI once received prophylactic antiarrhythmic therapy (lidocaine) to suppress ventricular tachyarrhythmias, the use of routine arrhythmia prophylaxis is inadvisable. Amiodarone is now favored (over lidocaine) in those with sustained symptomatic VT and in those who have survived VF. Although effective in suppressing ventricular tachyarrhythmias and even succeeding at times when amiodarone fails, lidocaine infusion increases risk of asystole.

Premature Ventricular Contractions

PVCs occur in almost all patients with MI, but their incidence declines rapidly with time. (Baseline rates are usually restored within 24 to 72 hours.) Isolated unifocal PVCs are of little importance. However, in the setting of acute infarction, consideration should be given to treating PVCs if they are frequent and precipitate angina or hemodynamic instability. Besides myocardial reperfusion, use of β-blockers and correction of electrolyte imbalances (keeping potassium >4 mmol/L and magnesium >2 mmol/L) will help a great deal. Intravenous followed by oral amiodarone may be used if the patient continues to have troublesome ventricular arrhythmias. Although expensive, intravenous amiodarone has replaced lidocaine as the drug of choice for ventricular arrhythmias because of its effectiveness and safety profile. Lidocaine should probably be reserved for young patients with good pump function and for those unusual patients refractory to amiodarone. For patients with hepatic disease, poor LV function, and high-grade AV block and for elderly patients, the risks of lidocaine usually exceed the benefits. In the skillfully monitored critical care unit, the development of early VT or VF is of little importance because it is corrected rapidly by electrical cardioversion.

Ventricular Tachycardia

For patients with acute ischemia, sustained VT occurs commonly within the first 48 hours and usually needs suppression. If the patient becomes hemodynamically unstable during an episode of VT, immediate DC cardioversion should be performed. If the rate is less than 150/min and patient remains relatively stable, antiarrhythmic therapy should be tried. Amiodarone is the drug of choice for control, initially given as a 150- or 300-mg bolus, followed by an infusion of 1 mg/min for 6 hour and 0.5 mg/min for 18 hours. Oral amiodarone is usually overlapped with intravenous form of the medication and should be continued for 3 to 6 months. Lidocaine infusion can also be used in this situation. It is given in bolus of 75 mg intravenously, followed by 50 mg every 5 minutes × 3 (for a total of 225 mg). Bolus doses of this agent rapidly achieve therapeutic concentrations. It is important to use lean body weight in calculating lidocaine doses to avoid toxicity. After loading, a continuous infusion of 1 to 2 mg/min is used for continued control. Because lidocaine is eliminated by the liver, patients with hepatic disease, CHF with passive hepatic congestion, and
advanced age can have a reduced rate of clearance. In such patients, the loading dose should be lowered to 75 to 125 mg and the infusion rate to 0.5 to 1 mg/min. Toxicity usually is manifest as either a CNS alteration (e.g., agitation, somnolence, seizures, confusion, muscle twitching) or cardiac effect (hypotension, bradycardia, sinus arrest). Plasma lidocaine levels probably should be monitored on a daily basis in patients at highest risk for lidocaine toxicity and should be spot-checked in all patients who exhibit CNS alterations compatible with lidocaine toxicity. For patients who are refractory to the effects of lidocaine in therapeutic doses, procainamide is given in an intravenous infusion at a dose of 20 mg/min loading dose until arrhythmia is suppressed, a total of 17 mg/kg is administered, hypotension occurs, or if QRS duration increases beyond 50%. Following the bolus, it is continued as an infusion at a dose of 1 to 4 mg/min. Procainamide can induce torsades de pointes in patients with hypokalemia, hypomagnesemia, LV dysfunction, and renal failure. Continuous monitoring of BP and ECG is necessary during its infusion.

Prompt myocardial reperfusion, β-blocker therapy, and correction of electrolyte and metabolic abnormalities are vital in restoring electrical stability in these patients.

One particular form of VT, IVR, deserves special mention. Usually self-limited, IVR is a series of wide QRS complexes of ventricular origin. When IVR occurs at a rate of 60 to 100 beats/min, it is termed “accelerated.” This rhythm most commonly occurs after reperfusion of ischemic myocardium or as an escape mechanism for patients with highgrade AV block. If perfusion is adequate, no treatment is indicated. Indeed, suppression may cause asystole.

VT that occurs within the first 48 hours has little impact on the patient's eventual outcome. However, that, which occurs after that time window, usually arises from LV dysfunction and carries increased risk of mortality. These patients must be revascularized to the extent possible and considered for defibrillator implantation.

**Ventricular Fibrillation**

VF occurs in up to 10% of all cases of MI and is responsible for 65% of all deaths. Most deaths occur in the prehospital phase of care, usually within the first hour of ischemia. An additional 15% to 20% of patients suffer VF after hospitalization. If applied promptly, DC cardioversion can correct more than 50% of episodes of acute VF due to AMI. Defibrillation is successful in less than 25% if applied after 4 minutes of onset of VF. VF carries little prognostic import if defibrillation is successful and if the disturbance occurs as an isolated electrical event early in the course of an MI (within first 24 to 48 hours). Like VT, VF occurring after the first 48 hours of an AMI usually occurs in the setting of poor LV systolic function and carries a poor longterm prognosis and must be considered for implantable cardioverter-defibrillators (ICD). Reversible factors increasing the risk of VF should be addressed promptly, and these include ongoing ischemia, electrolyte imbalances, anemia, hypoxemia, excessive catecholamine stimulation, or presence of pulmonary artery catheters or pacemakers in the heart. For refractory or recurrent VF, intravenous amiodarone or lidocaine is usually advisable after the initial resuscitation. Intravenous procainamide can be given in rare situations where the arrhythmia is refractory to lidocaine or amiodarone. Magnesium sulfate (1 to 2 g intravenously) has been advocated as a safe, prophylactic antiarrhythmic agent, particularly appropriate for patients with polymorphic VT or hypomagnesemia. Although magnesium is almost certainly safe in patients with normal renal function, commonly used doses are of questionable efficacy.

**Bradycardia**

Bradyarrhythmias occur more commonly in inferior and posterior MIs because of intense vagal stimulation and a higher incidence of sinoatrial (SA) and AV nodal ischemia resulting from occlusion of the right or circumflex coronary arteries. AV block and use of pacemakers are described in detail in Chapter 4. Bundle-
branch blocks and infranodal high-grade AV blocks that occur in the setting of an anterior MI carry poor prognosis because of the extent of myocardial damage and usually need permanent pacing if the patient survives. Acute right bundle-branch block (RBBB) occurs in about 5% of acute infarctions and is associated with increased mortality. Transcutaneous or transvenous pacing may be needed if there is symptomatic bradycardia. Acute LBBB, which complicates 1% to 5% of acute infarcts, is associated with a 25% rate of in-hospital mortality and pacing may be needed in these patients as well.

AF is not uncommon and is usually of acute onset. Acute and rapid AF can precipitate heart failure. The patient must be anticoagulated with IV heparin or enoxaparin (1 mg/kg SQ b.i.d.). Initially, the ventricular rate can be controlled with betablockers or calcium channel blockers. The patient should be cardioverted with IV amiodarone or by electrical means in situations of acute AF.

**Mechanical (Structural) Complications (Fig. 21-7)**

**Pericarditis/Tamponade**

Post-MI pericarditis can be divided conveniently into two distinct types: acute early pericarditis and delayed pericarditis (Dressler syndrome). The pain of pericarditis may be distinguished from that of continued or recurrent myocardial ischemia by its failure to radiate to distant sites, its poor response to antianginal therapy, the presence of a friction rub, and its sharp, pleuritic, or positional nature.

The ECG usually exhibits diffuse ST segment elevation not typically seen after occlusion of a major coronary artery. Histologic evidence of pericarditis occurs in almost all transmural MIs but usually is mild and clinically insignificant. Symptoms typical for pericarditis occur in only a small proportion of such cases. In the 10% of patients affected by acute pericarditis, symptoms usually emerge 2 to 4 days after the MI. Nonsteroidal anti-inflammatory drugs (e.g., aspirin and/or indomethacin) are helpful in controlling the inflammation and pain. Although effective as analgesic/anti-inflammatory agents, corticosteroids increase the risk of free ventricular wall rupture. Large pericardial fluid accumulations occur in fewer than 10%. Rarely, pericardial fluid may become hemorrhagic and accumulate sufficiently to cause tamponade in anticoagulated patients.

Delayed episodes of immunologically mediated febrile pleuropericarditis (Dressler syndrome) may complicate either MI or pericardiotomy any time within the subsequent 3 months. Dressler syndrome is much less common than acute pericarditis, occurring in only 1% to 3% of patients with MI. Leukocytosis and an elevated sedimentation rate are associated laboratory features. Pleural effusions are common in Dressler syndrome but rare in acute pericarditis. Because there is substantial risk of hemorrhagic pericarditis and tamponade in Dressler syndrome, anticoagulants are contraindicated. Indomethacin, with or without colchicines, may be used in the treatment of this condition.

Pump Failure with Cardiogenic Shock

Most in-hospital deaths from MI occur within 96 hours of admission secondary to shock resulting from LV failure. Assuming normal sinus rhythm, clinical evidence of heart failure develops when more than 20% of the LV sustains damage. (Persistent ST may be a hint of incipient heart failure if present longer than 48 hours after infarction.) Fatal pump failure usually ensues when more than 40% of the LV mass is infarcted or dysfunctional. The extent of lost muscle mass is a much more powerful determinant of outcome than the anatomic location of the infarct. Therefore, rapid myocardial reperfusion is the key to an optimal outcome. Contractility of ischemic but salvageable muscle may return after a period of hours to days (“stunned myocardium”). Ischemia-induced decreases in LV compliance usually require increased filling pressures to maintain stable cardiac output. Under most circumstances, a pulmonary capillary wedge pressure near 18 mm Hg is optimal.

Pulmonary edema should be treated with oxygen, noninvasive or invasive mechanical ventilation, diuretics, and inotropic drugs, as dictated by hemodynamics, mental status, and ventilatory parameters. Coronary angiography
with prompt revascularization by PCI or emergent coronary bypass surgery may be the only hope for most of these patients. Revascularization therapy may be particularly beneficial in those less than 75 years of age. Initial stabilization with IABP support is often helpful. IABP counterpulsations not only reduce afterload but also improve coronary blood flow. Because a substantial portion of the limited cardiac output must be diverted to the unsupported respiratory pump, mechanical ventilation can boost oxygen delivery to deprived vital organs and should be considered whenever respiratory distress becomes evident. Treatment of severe heart failure and cardiogenic shock is detailed in Chapter 3. Unfortunately, the prognosis for cardiogenic shock remains poor, with in-hospital mortality of 50% to 80%.

**Right Ventricular Infarction**

Some degree of right ventricular (RV) infarction is seen in up to 30% to 40% of all inferior Mls. Hypotension, jugular venous distension, the Kussmaul sign, and clear lung fields are key diagnostic characteristics. An important feature distinguishing RV infarct from pulmonary embolism is the rarity of dyspnea in the former condition. RV infarction may be confirmed electrocardiographically by ST segment elevation in right precordial leads (V₃R and V₄R). Pulmonary artery catheterization may be confirmatory when right atrial pressures are disproportionately elevated in relation to a wedge pressure. (Hemodynamic monitoring is also useful to exclude the presence of pericardial tamponade or constriction, which may have similar clinical appearance.)

RV infarction, usually the result of RCA occlusion, rarely occurs as an isolated event. Inferior LV infarction almost always accompanies an RV infarct because the RV, posterior interventricular septum, and inferior LV wall share a common blood supply.

The physiologic derangements of RV infarction closely parallel those of constrictive pericarditis and tamponade. As the RV fails, it dilates, restricting LV filling. This combination of reduced RV systolic function, RV dilation, and limited LV filling significantly reduces cardiac output. The presenting symptom of RV infarction is hypotension—not pulmonary edema. Therefore, the treatment of the RV infarct differs in several important respects from symptomatic LV infarction. As a priority, the filling pressure of the RV must be optimized. Ultrasonic evaluation of RV filling status is usually helpful in making this determination. Effective filling may initially require mean right atrial pressures higher than 20 mm Hg to maintain an acceptably high cardiac output. Once adequate RV filling has been ensured, cautious trials of inotropic drugs and/or afterload reduction also may prove helpful.

Conduction disturbances are very common in RV infarction. Because of the difficulty in achieving successful ventricular pacing and because of the substantial contribution of the atria to cardiac output during RV infarction, **sequential AV** pacing is often more successful than ventricular pacing alone. AF occurring during RV infarction is particularly detrimental because of reduced ventricular compliance and should be treated aggressively with electrical or chemical cardioversion.

Atrial infarction occurs rarely, usually in combination with infarction of the inferior wall of the LV. Fed by branches of the RCA, the right atrium is the most commonly affected chamber. Ischemia of the SA node and conduction pathways accounts for its most common manifestations: bradycardia, atrial arrhythmias, and heart block. Thrombi formed within the infarcted right atrium may embolize to the pulmonary artery.

**Acute Mitral Regurgitation**

Papillary muscle dysfunction or rupture is the most common mechanical complication of MI. In most cases, mild and transient MR is the result of papillary muscle ischemia or changes in LV geometry. MR has a wide range of presentations, however, ranging from minimal malfunction to frank rupture. MR most commonly results from malfunction of the posterior papillary muscle because it is fed by the single posterior descending artery, whereas the anterior papillary muscle is supplied by branches of both the LAD and circumflex arteries. Frank papillary muscle rupture is a rare but highly lethal event that carries
a 24-hours mortality rate near 70%. MR typically occurs 2 to 10 days after posterior or inferior MI and should be suspected in any patient with MI developing a new murmur (often at the cardiac apex).

The murmur of MR is often unimpressive; therefore, a high degree of suspicion should be maintained anytime a patient rapidly develops symptoms of left ventricular failure, especially when normal systolic function seems preserved. Regurgitant flow is greatest after papillary muscle rupture and less intense when dysfunction is caused by ischemia without structural damage. The diagnosis may be confirmed by echocardiography or pulmonary artery catheterization. Echocardiography (especially transesophageal studies) may reveal a hyperdynamic (unloaded) LV and flail mitral leaflet. (The surface echocardiogram may fail to detect small valvular defects.) Doppler studies may demonstrate the regurgitant left atrial jet. Invasive monitoring is indicated in almost all patients with MI who develop a new murmur, particularly if pulmonary congestion is present. Although pulmonary artery pressure tracings usually reveal large V waves produced by retrograde flow of blood across an incompetent mitral valve, V waves are much more sensitive than specific. VSD, mitral stenosis, or severe heart failure occasionally mimics MR by producing large V waves.

The primary objective in treating acute MR is to reduce left ventricular impedance (afterload). For stable patients with mild MR, LV afterload reduction may be sufficient. However, when florid pulmonary edema follows papillary muscle rupture, vasodilators (nitroprusside, nicardipine, or NTG) and intra-aortic balloon pumping should be followed immediately by surgery.

**Ventricular Septal Defect**

The ventricular septum ruptures in approximately 2% of all MIs. Predisposing factors for postinfarction VSD include an anterior-septal MI, hypertension, female gender, advanced age, and first infarction. VSD-related, left-to-right shunting reduces effective output and causes pulmonary edema. The anterior portion of the interventricular septum is supplied predominantly by a single vessel (the LAD), whereas the posterior portion is fed collaterally by several sources. Therefore, postinfarction VSD usually is a consequence of an anterior MI that involves the LAD. Conversely, VSD developing after a (true) posterior MI is a marker of diffuse multivessel disease and carries a worse prognosis.

For most patients, physical examination reveals biventricular heart failure and a new murmur. The new murmur usually is loud, harsh, holosystolic, and of maximal intensity at the left lower sternal border. An accompanying thrill is common. Pulmonary artery catheterization demonstrates a step-up in hemoglobin saturation between the right atrium and pulmonary artery (usually >10%). Diagnosis also can be made by left heart catheterization demonstrating movement of contrast from the LV to the RV. Hemodynamic compromise and magnitude of the left-to-right shunt parallel the size of the defect. Echocardiography may demonstrate a VSD, particularly if Doppler techniques and transesophageal imaging are used. A “bubble” echocardiogram (with agitated saline or optisonic contrast) occasionally shows bidirectional ventricular flow.

Therapy for a VSD depends on systemic and pulmonary capillary wedge pressures. Hypotensive patients with a low wedge pressure should receive fluids initially. If the blood pressure is maintained adequately and the wedge pressure is lower than 18 mm Hg, semielective surgical repair should be undertaken. Vasodilators may be useful if blood pressure remains adequate despite a low cardiac output and an elevated wedge pressure. If the patient is hypotensive with a high wedge pressure, temporary support by balloon pumping, inotropes, and vasodilators should precede immediate surgical correction. An increasingly sophisticated array of interventional devices (e.g., Amplatzer [Abbott Vascular, Santa Clara CA, USA], CardioSEAL [NMT Medical, Boston MA, USA]) is now available for percutaneous closure of a VSD. This alternative is an attractive alternative to surgery, especially in the most severely ill patients, for whom the surgical risk remains intimidatingly high.

Historically, the outcome of post-MI VSD has been very poor, with mortality mounting to approximately 90% at 2
months. However, the long-term results in patients undergoing successful early repair are excellent. Therefore, surgical repair at the earliest possible time after hemodynamic stabilization is desirable.

**Free Wall Rupture**

Almost invariably, rupture of the ventricular free wall proves rapidly fatal, as the patient succumbs to tamponade physiology. Although unusual (incidence between 2% and 8%), ventricular rupture occurs more commonly than either papillary muscle rupture or VSD; 10% of MI deaths result from free wall rupture. Most myocardial ruptures are early events; half occur within 4 days and almost all occur within 2 weeks after AMI. Hypertension accentuates wall stress and contributes to muscle disruption at the border of the normal and infarcted tissue. Ventricular rupture is most likely in elderly patients with extensive transmural damage and little collateral flow. Late fibrinolysis may hasten the occurrence of perforation. The clinical presentation of wall rupture usually is one of recurrent chest pain rapidly followed by neck vein distension, paradoxical pulse, shock, and death. ECG may show recurrent ST elevation or may not show any change at all. Differential diagnosis includes pericardial tamponade, tension pneumothorax, and massive muscle damage. Immediate thoracotomy must follow temporary stabilization with volume expansion, transfusion, and pericardiocentesis. Echocardiography may visualize a defect of the LV wall, free pericardial fluid, and diastolic right-sided cardiac collapse. Cardiac catheterization is not feasible for most patients and delays definitive surgical therapy, which is perhaps the only hope in many patients with this condition.

**Systemic Embolism**

The incidence of mural thrombi and arterial embolism may reach 30% in selected subsets of patients with MI. Large infarctions, particularly those involving the anterior and apical segments of the LV, predispose systemic embolism. Systemic embolism is less common now that many patients receive heparin and aspirin (with or without thrombolytic therapy) for AMI therapy. Patients with large infarctions, mural thrombi, or overtly dyskinetic segments on echocardiography should be anticoagulated, unless compelling contraindications exist.

**Role of ICD in Myocardial Infarction**

Patients who demonstrate sustained or nonsustained VT after the first 48 hours of AMI are at increased risk of SCD during and after discharge from hospital. Severe LV systolic dysfunction is also a marker of risk for SCD. An ICD device is implanted just like a pacemaker, and in fact, most of the currently available ICD models can also pace the heart for bradycardia. The ICD device monitors the rhythm, and if the patient goes into rapid VT, it is programmed to perform antitachycardia pacing, followed by delivery of DC shock if needed. If the patient drops into VF, it will deliver a shock immediately. The risk of SCD can be reduced significantly after revascularization and with use of adequate medical therapies (β-blocker, antiplatelet agents [clopidogrel and aspirin], statins, ACEI, and possibly also fish oils). The MADIT-1, MADIT-2, and MUSTT trials have helped form some guidelines for ICD implantation in post-MI patients.

The following are the guidelines for use of an ICD device following an MI:

1. Resuscitated VT/VF arrest after the first 48 hours of an MI
2. LV ejection fraction less than 35%, nonsustained VT on monitor, and inducible, nonsuppressible VT on EP study
3. LV ejection fraction less than 30% on echocardiography 1 month after MI, especially if the QRS duration is greater than 0.12 second

Incessant VT/VF episodes, those with class IV CHF, and those with other severe comorbid conditions (terminal cancer, lung, or liver disease) are considered contraindications for the ICD. Those with ischemic cardiomyopathy...
should ideally undergo revascularization procedures first (if they are candidates) and later be reevaluated for ICD. Patients who have suffered a large MI should undergo repeat echocardiography and possibly also 24- or 48-hours Holter monitoring 1 to 3 months after the event.

SUGGESTED READINGS


Chapter 22  
*Hypertensive Emergencies*

**Key Points**

1. Most cases of severe hypertension in the ICU do not stem from a new or exotic cause; rather, they are often the result of interrupting previously efficacious treatment for essential hypertension. Initial episodes of severe hypertension, however, clearly should be investigated for a secondary cause.

2. When organ failure accompanies severe hypertension, blood pressure (BP) generally should be reduced to safer (but not necessarily normal range) levels within minutes; in the absence of organ failure, reduction over hours to days is not only acceptable but also desirable.

3. Patients with chronic severe hypertension often do not tolerate rapid, profound BP reductions, because cerebral autoregulation is reset by chronic hypertension. More harm can be done by hypotension than persistent hypertension in these patients.

4. For most hypertensive crises requiring treatment, a mean arterial pressure of 110 mm Hg represents a reasonable initial BP target.

5. If immediate parenteral therapy is indicated for hypertensive crises with associated organ failure, sodium nitroprusside is in most cases the initial drug of choice. Nicardipine and labetalol are reasonable alternatives.

6. Oral therapy should be initiated early in the hospitalization to minimize the duration of parenteral therapy and ICU stay.

**DEFINITIONS**

Historically, the term “malignant hypertension” was defined as severe elevation of blood pressure (BP), advanced retinopathy, and papilledema. For patients meeting this definition, accompanying organ dysfunction was common but not universal. Similarly, “accelerated hypertension” was traditionally defined by comparable elevations of BP with lesser degrees of retinopathy in patients not exhibiting other organ damage. Unfortunately, these distinctions are artificial and not clinically useful. A simpler and more helpful approach is to classify hypertensive crises by the presence or absence of life-threatening organ damage. The urgency for treatment is based on organ dysfunction rather than on a specific blood pressure value. Similarly, the distinction between a hypertensive emergency and a hypertensive urgency is based primarily on the presence of target organ damage. When organ failure accompanies severe hypertension, restoration of a BP that approaches the chronic value should be accomplished within minutes to hours, whereas in cases of hypertension without organ failure, more gradual BP reduction over hours to days is prudent. Comorbid conditions as well as the pressure value often determine the speed and intensity of intervention. For example, blood pressure readings consistently above 160/105 mm Hg are usually addressed at a measured pace, but the same values recorded in a pregnant woman require prompt correction toward normal.

**PATHOPHYSIOLOGY**
Organ damage in hypertension is caused largely by small vessel (arteriolar) damage that results in platelet and fibrin deposition, loss of vascular autoregulation, and elevation of systemic vascular resistance (SVR). Hypertensive emergency is the consequence of elevated SVR, not of volume overload or high cardiac output. Because diastolic blood pressure varies with heart rate, a high diastolic pressure in a patient with relative bradycardia denotes greater vasoconstriction than the same pressure observed during tachycardia. In reality, unless there is renal failure, ongoing hypertension results in natriuresis and intravascular volume contraction. Therefore, the most efficacious hypertension treatments reduce afterload, not preload, and in some cases, intravenous volume expansion may even be necessary.

Although hypertension with a specific etiologic cause is rare in the general population, as many as half of all patients presenting for the first time with hypertension-induced organ failure are discovered to have an identifiable generating cause. Young patients (<30 years of age) and those of African descent are more likely to have one of these secondary (usually, renovascular or endocrine) causes. Most hypertensive crises encountered in the intensive care unit (ICU) are not, however, these newly discovered patients with secondary hypertension but rather patients, more commonly men, with known “essential” hypertension noncompliant with previously effective medical therapy. Cocaine or other recreational drug is often a contributing factor to the crisis. Regardless of the etiology, hypertension-induced organ failure is a serious problem. Historically, the majority of patients presenting with organ failure from hypertension were dead within a year of the diagnosis. Although the causes of death from hypertension have not changed (heart failure, myocardial infarction, stroke, and renal failure), mortality rates are now much lower in the setting of contemporary medical management.

The most common causes of hypertensive crises are antihypertensive drug withdrawal, autonomic hyperactivity, collagen vascular disease, recreational drugs, acute glomerulonephritis, head trauma, preeclampsia, and renovascular hypertension. In the surgical setting, hypertensive crisis may be encountered during cardiac surgery, major vascular reconstruction, neurosurgery, head and neck surgery, renal transplantation, or major trauma. These episodes are frequent in the early postoperative period and relate to increased sympathetic tone and vascular resistance. The incidence of postoperative hypertensive crisis varies based on the population studied.

Control of hypertension in patients with acute stroke is directed at maintaining adequate cerebral blood flow (CBF) to minimize ischemic damage and control intracerebral pressure. With adequate blood flow around the central area of the stroke or penumbra, cells may be salvaged. Thus, inappropriate lowering of blood pressure in acute stroke may increase neurological damage. If the patient with acute stroke requires thrombolytic therapy, goal systolic blood pressure is less than 185 mm Hg with end diastolic blood pressure held less than 100 mm Hg to decrease the risk of bleeding. Other indications for acute blood pressure control include systolic blood pressure greater than 220 mm Hg or diastolic blood pressure greater than 120 mm Hg. Initial goal is 15% to 20% reduction in mean arterial pressure over 24 hours. In the presence of intracranial hemorrhage, systolic blood pressure is decreased within 12 to 24 hours to less than 180 mm Hg or a mean arterial pressure less than 130 mm Hg.

HISTORY AND PHYSICAL EXAMINATION

The goals of the history and physical are to distinguish hypertension that requires immediate treatment from that to be corrected more gradually and to define the reason for the crisis. Obtaining a history of long-standing hypertension, antihypertensive drug use, or illicit or over-the-counter drug use is critical. Knowledge of preexisting organ failure also helps define the urgency of therapy. (Patients with well-
established chronic renal failure do not require the same haste for BP control as those acutely developing a
similar elevation in serum creatinine.) Most patients with hypertensive crises are symptomatic but have
nonspecific complaints. Cardiac symptoms (e.g., angina, congestive heart failure) and dyspnea are
frequent, whereas nausea, vomiting, and focal neurological deficits are distinctly uncommon. Headache
occurs in approximately 85% of patients, and blurred vision occurs in more than 50%. When headache and
confusion are accompanied by visual loss and seizures in association with characteristic brain MRI findings,
this grouping is termed the posterior reversible encephalopathy syndrome (PRES).

BP should be measured in all four limbs using an appropriate-size cuff. Failure to compare upper to lower
extremity BP risks missing aortic coarctation or distal dissection, whereas failure to detect asymmetrical arm
BP risks missing proximal aortic dissection. Surprisingly, many patients presenting with severe hypertension
exhibit orthostatic symptoms because of pressure-induced diuresis. Physical examination should devote
special attention to inspection of the ocular fundus and to examination of the neurologic and
cardiopulmonary systems. Retinopathy is a sensitive indicator of hypertension-induced organ injury.
Papilledema, exudates, flame hemorrhages, and arteriolar constriction characterize the retinopathy
traditionally associated with malignant hypertension and correlate well with renal involvement. After control
of BP, retinal hemorrhages and papilledema resolve or heal over

weeks to months. Confusion can be an important sign of hypertensive encephalopathy or ischemic or
hemorrhagic stroke. Examination of the heart can reveal enlargement and a fourth heart sound with long-
standing hypertension and a third heart sound in the presence of left ventricular decompensation. Murmurs
of aortic or mitral insufficiency are important to identify as potential causes of pulmonary edema. Detection
of an abdominal bruit, suggestive of renal artery stenosis, is an uncommon but critical physical finding.
Laboratory examination should include urinalysis, electrocardiogram, chest radiograph, CT scan of the
head, complete blood count, and determination of electrolytes and creatinine. Evidence of left ventricular or
atrial enlargement is common, occurring in about a quarter of patients. Moderate renal insufficiency (i.e.,
serum creatinine >3.5 mg/dL) is present in about one fourth of cases. In patients with an elevated
creatinine, urinalysis commonly shows proteinuria, hematuria, and red cell cast formation. The peripheral
blood smear may demonstrate microangiopathic hemolysis. Hypokalemic alkalosis frequently occurs as a
result of secondary hyperaldosteronism consequent to diuretic usage but could be a clue to primary
hyperaldosteronism.

TREATMENT PRINCIPLES

Hypertension with Organ Failure (Hypertensive Emergency)
The aggressiveness of therapy should be guided by chronicity of the condition and evidence for organ damage,
not by BP values alone. In fact, most patients with “severe hypertension” defined as a systolic BP greater than
160 mm Hg or a diastolic BP greater than 100 mm Hg have no acute organ dysfunction (thus, hypertensive
urgency), and no overt organ injury until systemic pressures exceed 220/130 mm Hg. A significant exception to
this rule is the pregnant patient, in whom end-organ effects may be seen with diastolic values as low as 100 mm
Hg. In pregnancy-related hypertension, intravenous drug therapy is reserved for patients with persistent systolic
blood pressure greater than 180 mm Hg or persistent diastolic blood pressure greater than 110 mm Hg. Prior to
delivery, it is desirable to maintain diastolic blood pressure greater than 90 mm Hg. This pressure allows for
adequate uteroplacental perfusion. If diastolic blood pressure falls to less than 90 mm Hg, decreased
uteroplacental perfusion may precipitate acute fetal distress that may progress to death in utero or to perinatal
asphyxia. Hypertensive patients requiring immediate treatment should be admitted to an ICU for closely
monitored therapy including cardiac performance, urine output, and neurologic status. If there are doubts
regarding the accuracy of noninvasive measurements, an arterial catheter can be inserted, but one is not routinely necessary.

Surprisingly, given the incidence of severe hypertension, there are no studies which demonstrate convincing superiority of one drug class over another with regard to organ protection or survival. Given the lack of proven advantage with a particular treatment, drug selection is typically made based on patient characteristics and physician preference. The ideal emergency antihypertensive would be potent, titratable, intravenous, and rapid but shortlived and would act by reducing afterload. Sodium nitroprusside and nicardipine fit this description. The advantages and disadvantages of commonly used drugs for severe hypertension treatment are shown in Table 22-1. Whenever possible, oral therapy should be initiated concurrently to minimize the duration of IV therapy and ICU stay.

Altered vascular autoregulation occurs in patients in hypertensive crisis. Because end-organ damage is already present, rapid and excessive correction of blood pressure may further reduce perfusion and potentiate injury. The initial goal of therapy in hypertensive emergencies is to reduce mean arterial blood pressure by no more than 25% within minutes to 1 hour and, if stable, to 160/100 to 110 mm Hg within the next 2 to 6 hours. Sodium and volume depletion may be significant, and gentle volume expansion with saline helps restore organ perfusion and prevent abrupt decline in blood pressure when antihypertensive agents are provided.

**Hypertension Without Organ Failure (Hypertensive Urgency)**

Although important, hypertension occurring in the absence of organ failure does not indicate the same seriousness as when organ failure is present. In this setting, a reasonable goal is to reduce mean arterial BP by approximately 15% to 20% and to achieve a diastolic value near 110 mm Hg over a 24- to 48-hour period. Subsequent normalization of BP over days to weeks is safe and averts complications associated with rapid or excessive reductions. These patients do not require hospitalization and should be managed with oral agents. Captopril, labetalol, and clonidine are useful drugs for hypertensive urgencies that can be used to gradually, smoothly, and effectively lower blood pressure (Table 22-2).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical Dosing</th>
<th>Site of Action</th>
<th>Advantages</th>
<th>Side Effects/Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clevidipine</td>
<td>Begin 1-2 mg/h Increase in 1-2 mg/h increments every 5-10 min up to 32 mg/h</td>
<td>L-type Ca²⁺ blocker, arterial dilator</td>
<td>Rapid onset Rapid offset Plasma metabolism</td>
<td>Vomiting Time-limited refrigerated emulsion Expensive</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Begin 500 μg/kg load with 25-50 μg/kg/min infusion Increase in 25 μg/kg/min increments every 10 min to max 300 μg/kg/min</td>
<td>β-blocker</td>
<td>Rapid onset Antiarrhythmic Rapid offset</td>
<td>Exacerbates CHF and asthma Cardiac conduction block Nausea</td>
</tr>
<tr>
<td>Drug</td>
<td>Initial Dose/Infusion</td>
<td>Increment Details</td>
<td>Mechanism/Action</td>
<td>Side Effects/Precautions</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>Begin 1.25 mg every 6 h</td>
<td>Increase by 1.25-mg increments with each subsequent dose to max of 5 mg q6h</td>
<td>Angiotensin-converting enzyme (ACE) inhibitor</td>
<td>Effective in high-renin states Hypotension in volume depleted May exacerbate renal failure Headache Contraindicated in pregnancy</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>Begin 0.1 μg/kg/min infusion</td>
<td>Increase in 0.1-1 μg/kg/min increments every 15 min to max 1.6 μg/kg/min</td>
<td>Dopamine-1 agonist</td>
<td>Increased renal blood flow Expensive</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Begin 10-20 mg bolus every 30 min</td>
<td></td>
<td>Direct dilator (arterial &gt; venous)</td>
<td>No CNS effects Reflex tachycardia Overshoot hypotension Headache Vomiting</td>
</tr>
<tr>
<td>Labetalol</td>
<td>20-mg boluses at 15-min intervals as needed or 20-mg bolus followed by 1-2 mg/min infusion Increase in 2 mg/min increments every 10-15 min</td>
<td>α- and β-blocker</td>
<td>No “overshoot” hypotension Preserved cardiac output</td>
<td>Exacerbates CHF and asthma Cardiac conduction block Tolerance with prolonged use</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Begin 5 mg/h</td>
<td>Increase in 2.5 mg/h increments every 10-15 min up to 15 mg/h</td>
<td>Ca²⁺ blocker Arterial dilator</td>
<td>Rapid onset Easy to titrate Coronary dilator Reflex tachycardia Headache</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Begin 5 μg/min</td>
<td>Increase in 5-10 μg/min increments every 5-10 min up to 200 μg/min</td>
<td>Direct dilator (venous &gt; arterial)</td>
<td>Coronary dilator Rapid onset Weak arterial dilator Headache Ethanol vehicle Absorbed by some IV tubing</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>Begin 0.25 μg/kg/min</td>
<td>Increase in 1-2 μg/kg/min increments every 5-10 min up to 10 μg/kg/min</td>
<td>Direct dilator (balanced)</td>
<td>Rapid onset Easy to titrate Nonsedating Rapid offset Thiocyanate /cyanide toxicity Reflex tachycardia Vomiting Light sensitive</td>
</tr>
</tbody>
</table>
Phentolamine 1-5-mg boluses  \( \alpha \)-blocker +
direct vasodilator Excellent for adrenergic crisis Rapid onset
Tachycardia Angina Vomiting Tachyphylaxis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Subsequent Doses</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>0.1-0.2 mg orally</td>
<td>0.1 mg every 1 h to maximum dose of 0.7 mg</td>
<td>8-12 h</td>
</tr>
<tr>
<td>Nifedipine(^a)</td>
<td>10 mg orally</td>
<td>10-20 mg every 15 min</td>
<td>3-6 h</td>
</tr>
<tr>
<td>Captopril(^a)</td>
<td>12.5-25 mg</td>
<td>25 mg every 8 h</td>
<td>6-8 h</td>
</tr>
</tbody>
</table>

\(^a\)Use with extreme caution.

An elevated BP alone does not necessarily require invasive monitoring or parenteral treatment. In fact, when hypertension is the result of cocaine, amphetamine, or phencyclidine ingestion, antihypertensive drugs may not even be needed; withholding the offending agent and providing judicious benzodiazepine sedation often suffice. Because many of these cases are the result of noncompliance with a previously effective regimen, merely restarting the patient's outpatient medications is frequently effective. It is important to identify the reasons for noncompliance because if it is due to prohibitive drug costs or intolerable side effects (e.g., sedation, fatigue, or impotence), the problem is likely to be repeated.

**SPECIFIC HYPERTENSIVE PROBLEMS**

A summary of preferred therapy for various hypertensive emergencies is presented in Table 22-3; however, a brief discussion of the most common hypertensive situations below helps emphasize the unique aspects of pathophysiology and treatment.

**Hypertensive Encephalopathy**

Hypertensive encephalopathy is diffuse brain dysfunction caused by cerebral edema resulting from the loss of central nervous system (CNS) vessel autoregulation. The rate at which the BP increases probably is as important as the absolute level achieved. In chronic hypertension, changes in cerebral autoregulation tend to reduce the risk of hypertensive encephalopathy, even with marked elevations in BP. By contrast, an acute BP rise during pregnancy or an episode of glomerulonephritis may cause encephalopathy with a BP as low as 160/100 mm Hg.

Hypertensive encephalopathy must be distinguished from the much more common mental status-altering disorders, including ischemic or hemorrhagic stroke, hypoglycemia, subarachnoid hemorrhage, meningitis, encephalitis, brain tumors, and seizures. Distinction may be difficult because many of these conditions may be accompanied by secondary elevations of BP. Headache is the most common complaint, followed by nausea, vomiting, blurred vision, and confusion. Focal neurological deficits, including hemiparesis and cranial nerve palsies (particularly of the facial nerve), may occur but are uncommon. Arteritis of the vessels nourishing the
optic nerve (not increased intracranial pressure) produces the papilledema seen in most cases of hypertensive encephalopathy. There are no specific laboratory findings in hypertensive encephalopathy; the electroencephalographic features are nondiagnostic, and although the opening pressure recorded during a lumbar puncture may be elevated, the fluid analysis usually is unremarkable.

The *sine qua non* of hypertensive encephalopathy is mental clearing within hours of BP control. Therefore, the goal of therapy is to lower the BP to “safe” levels as quickly as possible with agents such as nitroprusside or nicardipine. A diastolic BP of 100 to 110 mm Hg is an appropriate initial target. Normally, CBF is autoregulated to maintain constant perfusion over a wide range of mean arterial pressures (Fig. 22-1).

Failure of cerebral autoregulation may allow excessive perfusion (resulting in cerebral edema) or transient periods of hypoperfusion and ischemia. Normal regulatory mechanisms are modified by the presence of chronic hypertension, making higher mean arterial pressures necessary for adequate cerebral perfusion. Therefore, it is important not to lower perfusion pressure excessively in any hypertensive CNS syndrome.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Preferred Drugs</th>
<th>Drugs to Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissecting aneurysm</td>
<td>Nitroprusside + β-blocker</td>
<td>Direct vasodilators alone (nitroprusside, hydralazine)</td>
</tr>
<tr>
<td></td>
<td>Nicardipine ± β-blocker</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Labetalol</td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Nitroprusside</td>
<td>β-Blockers&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Nitrates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nicardipine</td>
<td>Labetalol</td>
</tr>
<tr>
<td></td>
<td>Fenoldopam</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diuretics</td>
<td></td>
</tr>
<tr>
<td>Angina/MI (without CHF)</td>
<td>β-Blockers</td>
<td>Direct vasodilators alone (nitroprusside diazoxide, hydralazine)</td>
</tr>
<tr>
<td></td>
<td>Nitrates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nicardipine</td>
<td>Phentolamine</td>
</tr>
<tr>
<td></td>
<td>Calcium blockers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Labetalol</td>
<td></td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>No treatment (?)</td>
<td>Clonidine</td>
</tr>
<tr>
<td></td>
<td>Nitroprusside</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nicardipine</td>
<td></td>
</tr>
<tr>
<td>Hypertensive encephalopathy</td>
<td>Nitroprusside</td>
<td>Clonidine</td>
</tr>
<tr>
<td></td>
<td>Nicardipine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Labetalol</td>
<td>Reserpine</td>
</tr>
<tr>
<td></td>
<td>Fenoldopam</td>
<td>β-Blockers</td>
</tr>
</tbody>
</table>
Catecholamine excess
Phentolamine
Nicardipine
Nitroprusside + β-blocker
Benzodiazepine as adjunct

β-Blockers alone
Labetalol

Postoperative HTN
Nitroprusside
Nicardipine
Esmolol

Long-acting agents

Preeclampsia
Labetalol
Nicardipine

Angiotensin-converting enzyme inhibitors

*Exception: β-Blockers useful in pulmonary edema from diastolic dysfunction.

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**FIGURE 22-1. Effects of mean arterial pressure on CBF.** Although CBF normally is autoregulated in the range of 50 to 150 mm Hg, chronic hypertension shifts this curve rightward and necessitates a higher minimal pressure for adequate flow.

**Cerebral Ischemia and Hemorrhage**

Hypertension predisposes to three specific “stroke syndromes”: bland cerebral infarction, subarachnoid hemorrhage, and intracerebral hemorrhage. Sudden onset of focal neurologic deficits, obtundation, headache, and vomiting are the most frequent symptoms of these disorders. (Focal deficits are less common with subarachnoid hemorrhage.) In all three situations, vascular autoregulation is lost in areas of acute bleeding or infarction, and typically in the period surrounding a stroke, BP rises probably as a protective mechanism against ischemia. Although the mechanism is uncertain, it is clear that transient hypertension often resolves within 7 to 10 days of the event and this modest hypertensive response is not harmful.
BP manipulation in patients with stroke remains controversial (see Chapter 34). Current expert recommendations are that BP should not be reduced unless thrombolytic therapy is planned, or BP exceeds 220/120 mm Hg, or there is evidence of extracerebral organ damage. Opposing this advice are data suggesting that reducing BP greater than 180/110 mm Hg may decrease the risk of transforming ischemic to hemorrhagic strokes. It is clear that excessive or very rapid reductions in BP may worsen CNS deficits. Therefore, cautious lowering of the diastolic BP to approximately 110 mm Hg is a reasonable goal.

Without a predisposing anatomic abnormality, hypertension alone rarely results in subarachnoid hemorrhage. In clinical trials of antihypertensive therapy in subarachnoid bleeding, mixed results have been observed. BP reductions halve the risk of rebleeding but increase the risks of ischemic infarction. Hence, therapy is usually withheld unless the systolic BP exceeds 160 mm Hg or mean arterial pressure is greater than 110 mm Hg. Arterial vasospasm, a process that further reduces perfusion, is common several days to a week after subarachnoid hemorrhage. The calcium channel blocker nimodipine is efficacious in subarachnoid hemorrhage even in the absence of BP reduction. In contrast to its relatively minor role in the causation of subarachnoid hemorrhage, hypertension is a major predisposing factor for intracerebral hemorrhage, especially in patients receiving systemic anticoagulation. In patients with parenchymal bleeding, blood often enters the subarachnoid space (mimicking subarachnoid hemorrhage) by dissecting through the internal capsule or putamen into the lateral ventricles. In this circumstance, it makes sense to reduce systolic pressure less than 140 mm Hg.

When urgent reduction in BP is indicated in any of these three conditions, the short-acting agents, nitroprusside, nicardipine, and labetalol, are favored drugs. Because of the sedating effects of clonidine, which compromise assessment of mental status, this agent is not typically used first. Nifedipine, hydralazine, and angiotensin-converting enzyme (ACE) inhibitors are not good initial choices because of the difficulty in controlling response.

### Aortic Dissection

Aortic dissection should be suspected in the setting of profound hypertension when patients have chest or back pain, an arm/leg BP difference, absent pulses in the lower extremities, or asymmetry in BP between arms. Chest and abdominal imaging as well as EKG recording provide essential data. A history of cocaine use should heighten suspicion of dissection even in young patients. Artifactual hypotension may result if BP is checked only in the left arm of a patient with aortic dissection as blood flow to the left subclavian artery is compromised. The diagnosis of aortic dissection is supported by finding a widened mediastinum on chest radiograph. Confirmation comes from computed tomography (CT), magnetic resonance imaging (MRI), or aortography. The goal is to immediately decrease both mean BP and the rate of increase in systolic pressure (ejection velocity) while preserving vital organ perfusion. A target systolic BP of approximately 120 mm Hg usually is appropriate. β-Blockade is quite effective at reducing ejection velocity, but unfortunately β-blockers alone usually do not provide a sufficiently rapid reduction in BP. Because direct vasodilators alone (e.g., hydralazine, nitroprusside, and diazoxide) increase heart rate, cardiac output, and ejection velocity, they represent suboptimal choices for therapy. Therefore, β-blockers may be used in conjunction with a vasodilator-like nitroprusside or nicardipine. Alternatively, a combined α- and β-blocker (e.g., labetalol) can be used.

Vascular surgery consultation is prudent even though many cases are now managed with percutaneous graft (stent) placement. In proximal dissection, after BP is controlled, surgical intervention is indicated, and although surgery is not necessary in most cases of distal dissection, compromise of blood flow to a limb or leakage may require surgical intervention.

### Renal Failure

Renal disease may be the cause of hypertension, as with glomerulonephritis, vasculitis, or renal artery stenosis, or may be the result of damage from a hypertensive crisis. When hypertension is the cause of kidney injury,
reversible perfusion-related increases in creatinine and blood urea nitrogen (BUN) frequently follow BP reduction. Nevertheless, reestablishing a safe BP is the main priority. Although other reversible causes of renal insufficiency (volume depletion, renal artery occlusion, lower tract obstruction) should be considered, an increasing BUN or creatinine value should not deter the clinician from continuing antihypertensive therapy. For patients presenting with a serum creatinine exceeding 3.5 mg/dL, acute progression of kidney injury is a likely and often unavoidable consequence of therapy. In renal insufficiency, nitroprusside is a good drug for BP control, even though thiocyanate toxicity is a concern; if patients are quickly transitioned to oral therapy, toxicity is rarely a problem. Labetalol, nicardipine, and fenoldopam represent good alternatives.

### Pulmonary Edema

In many if not most cases of severe hypertension, pulmonary edema is primarily the result of excessive left ventricular afterload or acutely worsened diastolic dysfunction, not excessive circulating volume, and usually responds rapidly when SVR is lowered. An exception to this rule is the patient with dialysis-dependent renal failure who may have volume-dependent hypertension. Heightened afterload is most likely to cause pulmonary edema in patients with preexisting left ventricular dysfunction (including diastolic dysfunction) or aortic or mitral insufficiency. Effective therapy focuses on reduction of afterload, making nitroprusside and nicardipine useful agents. Nitroglycerin is particularly useful in hypertensive patients with volume overload and myocardial ischemia. In clearly volume-overloaded patients, morphine sulfate, diuretics, and hemofiltration are useful adjuncts.

### Angina and Myocardial Infarction

During acute myocardial ischemia, reductions in BP preserve endangered myocardium by reducing afterload, decreasing wall stress, and increasing myocardial perfusion. In severe hypertension with cardiac ischemia, arterial vasodilators that produce tachycardia and thereby increase myocardial oxygen consumption (e.g., hydralazine, diazoxide, minoxidil) should be avoided. Caution also should be exercised when using nitroprusside, a drug that tends to divert blood away from the most ischemic areas of the heart. Labetalol, nicardipine, and β-blockers are attractive therapeutic options because they improve the ratio of oxygen supply to demand. Nitroglycerin is much more a venodilator than arterial dilator; hence, when administered alone, it is rarely sufficient to control BP. Nevertheless, at high-end doses, it dilates both peripheral and coronary arteries, thereby reducing preload, decreasing BP, and increasing myocardial blood flow.

### Catecholamine Excess

Conditions resulting in catecholamine-induced hypertension include (1) pheochromocytoma, (2) sympathomimetic illicit drugs (cocaine, lysergic acid diethylamide [LSD], phencyclidine, and amphetamines), (3) monoamine oxidase inhibitor (MAOI) crisis, and (4) antihypertensive withdrawal (rebound) syndrome. Patients with these disorders commonly present with tachycardia, diaphoresis, pallor, pounding headache, and vomiting. Pheochromocytoma is a rare cause of hypertensive crisis but should be considered in patients with hypertension induced by performance of angiography or the induction of anesthesia and in patients with a history of hyperparathyroidism or a family history of pheochromocytoma (see Chapter 32). MAOI crisis is also rare, occurring when tyramine-containing foods (cheese, beer, wine, chocolate) or other sympathomimetic agents are ingested by patients receiving MAOI antidepressants. (The antibiotic linezolid also has MAOI properties.) The problem of rebound hypertension is especially common in postoperative patients and those in the ICU after abrupt discontinuation of antihypertensive drugs. Although this syndrome is most frequently associated with the centrally acting α-agents (e.g., clonidine and methyldopa), withdrawal of β-blockers also may produce rebound hypertension. When a sympathomimetic drug is the cause of hypertensive crisis, control of
agitation with a benzodiazepine and tincture of time are often the only needed treatments.

If treatment of any of these syndromes is required, α-adrenergic blockers (e.g., phentolamine) or direct vasodilators (e.g., nitroprusside) are the mainstays of therapy. Nicardipine and fenoldopam are useful alternatives. Used alone, β-blockers are contraindicated in catecholamine excess because unopposed α-adrenergic effects may paradoxically worsen hypertension. The same problem may also be encountered with labetalol because its β-blocking effects are substantially more prominent than its α-blocking actions.

**Preeclampsia/Eclampsia**

Eclampsia is defined as the occurrence of hypertension, edema, proteinuria, and seizures in the last trimester of pregnancy. (Lacking seizures, the syndrome is termed preeclampsia.) Although the specific cause of eclampsia is unknown, the syndrome responds to delivery of the infant. Most patients have significant elevations in SVR and intravascular volume depletion with hemoconcentration (even patients with edema). Based upon very limited data, the recommended target is BP of 140 to 160 systolic and 90 to 105 mm Hg diastolic. In addition to magnesium (4 to 6 g IV over 1 hour followed by 1 to 2 g/h IV), specific antihypertensive therapy should be initiated. There are no good data on the comparative safety or effectiveness of antihypertensives in pregnancy, although it is generally accepted that ACE inhibitors should be avoided. Hydralazine has been a traditional therapeutic choice but is not ideal because of difficulty in titrating the response and the frequency of side effects. Calcium channel and β-blockers have generally been considered safe. For severe hypertension, labetalol, nicardipine, or nitroprusside are effective. (Because of its chemical composition, there is substantial emotion regarding the use of nitroprusside in pregnancy but little data to suggest that the drug is unsafe.) Diuretics can be used if there is convincing evidence of intravascular volume expansion. As is always the case in pregnancy, the risks of any chosen therapy must be weighed against benefits and potential alternatives.

**THERAPY FOR HYPERTENSIVE EMERGENCIES**

**Commonly Used Agents**

**Diuretics**

Because most patients with severe hypertension have normal or reduced circulating blood volume, diuretics should be avoided in the emergency setting unless overt signs are present of heart failure, pulmonary edema, or fluid overload. Although not intuitive, volume supplementation with isotonic saline often is necessary when using potent vasodilators to correct hypertensive crises. (With more chronic use, however, most antihypertensive agents tend to cause sodium retention and should be used in conjunction with a diuretic.) IV furosemide is the most commonly used diuretic because it is potent, rapidly acting, and inexpensive and provides mild vasodilation. Bumetanide is essentially equivalent.

**Nitroprusside**

Nitroprusside is a direct-acting arteriovenous dilator with an immediate onset of action (usually <1 minute) and the potential for rapid termination of action (1 to 3 minutes). Nitroprusside effects are mediated by the vascular release of the endogenous vasodilator, nitric oxide. The photoinstability of nitroprusside mandates frequent changes of solutions and use of light-protected containers. Infusion, typically, is initiated at a dose of 0.5 μg/kg/min and titrated upward at 5- to 10-minute intervals to produce the desired BP. Doses required for hypertension often are higher than those needed for the treatment of congestive heart failure but should not exceed 10 μg/kg/min. Because of its potency, controlled administration by infusion pump is mandatory, and an arterial catheter for blood pressure measurement should be seriously considered. At low dosage rates, reductions in SVR are offset by increases in cardiac output. Therefore, BP may remain stable initially despite a beneficial action; reduction of BP often requires higher range dosing. The effects of nitroprusside are most
pronounced in patients taking multiple other antihypertensive drugs and those who are volume depleted. Nitroprusside (which is approx. 40% cyanide) is metabolized hepatically to cyanogen and then to thiocyanate, which is then cleared by the kidney. Therefore, hepatic failure may result in cyanide toxicity, and renal failure may lead to thiocyanate toxicity. Cyanide levels higher than 10 mg/dL may cause hepatic failure, metabolic acidosis, dyspnea, and vomiting. Administration of nitroprusside at this dose may produce cyanide at a greater rate than humans can detoxify. The initial starting dose should be 0.5 μg/kg/m, titrated as tolerated. The duration of treatment should be a short as possible, and the infusion rate should not exceed 2 μg/kg/m. Nitrates, cyanocobalamin (vitamin B₁₂), and thiosulfate are useful in the treatment of thiocyanate toxicity (see Chapter 38).

**Calcium Channel Blockers**

Calcium channel blockers produce systemic and coronary vasodilation by inhibiting slow calcium channels. Verapamil, the first parenteral calcium channel blocker, causes myocardial depression and conduction blockade in a substantial number of patients, even though it promptly but briefly lowers BP after a single IV dose. Because of its negative inotropic action and because cardiac conduction is so often impaired, resulting in a slower heart rate, increased PR interval, and occasionally second-degree and third-degree atrioventricular blocks, verapamil represents a relatively poor choice for acute hypertension treatment. Because nifedipine is not available IV and oral use often results in precipitous, dangerous declines in BP, it should not be used in hypertensive crises.

Nicardipine, a parenteral calcium channel blocker, rapidly (within 5 to 15 minutes) reduces BP when administered by continuous infusion at rates of 5 to 15 mg/h. Unlike its predecessor, verapamil, cardiac contractility and conduction rarely are adversely affected. Increases in ejection fraction and stroke volume are responsible for the rises in cardiac output observed in most patients. Reflex tachycardia stemming from vasodilation rarely is a problem, making this drug an excellent alternative to nitroprusside in cases of hypertension associated with myocardial ischemia or congestive heart failure.

The onset of action for intravenous nicardipine is 5 to 15 minutes and its duration of action is 4 to 6 hours. Intravenous nicardipine has been shown to reduce both cardiac and cerebral ischemia. Dosage is independent of body weight. Nicardipine is given at an initial infusion rate of 5 mg/h, increasing by 2.5 mg/h every 5 minutes to a maximum of 15 mg/h until the desired blood pressure reduction is realized.

Clevidipine is among the newest IV calcium channel blockers. It is an arteriolar dilator with the theoretical advantage of being metabolized by plasma esterases, hence not subject to changes in hepatic or renal function. Clevidipine safely decreases blood pressure and heart failure and does not cause unexpected hypotension. It is safe and effective in renal disease complicated by severe hypertension. Because clevidipine is rapidly metabolized, it is a relatively safe alternative in patients with severe renal disease with or without dialysis. Its properties and clinical performance suggest clevidipine may be a logical and attractive drug for hypertensive emergencies. This drug can be safely used as an infusion for up to 96 hours.

**β-Blockers**

Esmolol is a β-blocker with a very short duration of action because of its rapid hydrolysis in the blood. Because esmolol begins to act within 1 minute and lasts only 10 to 20 minutes after stopping infusion, it is a nearly an ideal agent for control of supraventricular arrhythmias and hypertension, provided β-blockade is not contraindicated. An initial loading dose of 500 to 1,000 μg/kg is followed by a constant infusion of 25 to 50 μg/kg/min titrated upward every 10 to 20 minute until control is achieved. It is rare to require infusions exceeding 300 μg/kg/min. Toxicity is related to β-blockade (e.g., bradycardia, conduction abnormalities, and low cardiac output). Patients with chronic obstructive pulmonary disease may experience bronchospasm.
Labetalol is a combined $\alpha$- and $\beta$-blocker with rapid onset but a long and variable duration of action (2 to 4 hours). The $\beta$-blocking properties of labetalol are substantially more potent than its $\alpha$-blocking effects, occasionally resulting in paradoxical hypertension in high catecholamine states. Advantages of labetalol are the rarity of “overshoot hypotension” and impairment of cardiac output. An initial bolus of 20 mg is almost always effective in lowering BP within 2 to 5 minutes, whereas doses of 20 to 80 mg at 20- to 40-minute intervals provide continued BP control. An alternative to repeated boluses is a continuous infusion of 1 to 2 mg/min. Labetalol also is available orally, facilitating conversion from IV dosing. The primary disadvantages of labetalol lie in its potential to exacerbate heart failure and bronchospasm and its long duration of action.

**Fenoldopam**

Fenoldopam is a short-acting, hepatically cleared, dopamine receptor agonist that lowers BP and increases renal blood flow, thereby causing natriuresis. An initial dose of 0.1 $\mu$g/kg/min followed by an initial infusion of 0.05 to 0.1 $\mu$g/kg/min titrated upward to a maximum of 1.6 $\mu$g/kg/m. This agent controls BP over 1 to 3 hours. Initial antihypertensive effects occur within 5 to 10 minutes. Reflex tachycardia is common. Fenoldopam improves creatinine clearance, urine flow rates, and sodium excretion in the severely hypertensive patient with both normal and impaired renal function. It may cause a dose-dependent increase in intraocular pressure and should be avoided in patients with risk factors for intraocular and intracranial hypertension.

**Nitrates**

Nitroglycerin is primarily a venodilator having an immediate onset but brief duration of action. Because patients with hypertensive crises are often volume depleted, and venodilation is much more prominent than peripheral arterial dilation, nitroglycerin often causes cardiac output to decline. Because it is not a potent arterial vasodilator, nitroglycerin must usually be combined with other classes of drugs like $\beta$-blockers or calcium channel blockers for effect. Nitroglycerin is particularly useful in the setting of hypertensive myocardial ischemia with congestive heart failure or pulmonary edema. Initial doses of 5 to 10 $\mu$g/min are reasonable. Liver disease reduces the hepatic metabolism of nitrates potentiating their effects. The side effects of nitrates include headache, tachycardia, and flushing but rarely are dose limiting. Nitroglycerin is not an acceptable primary therapy for management of hypertensive emergencies.

**Angiotensin-Converting Enzyme Inhibitors**

Angiotensin-converting enzyme (ACE) inhibitors prevent conversion of angiotensin I to the extremely potent vasoconstrictor angiotensin II. Reductions in SVR with stable pulmonary capillary wedge pressures and cardiac outputs usually are typical after ACE administration, although patients with congestive heart failure may have a fall in filling pressures and a rise in cardiac output. There are a host of oral ACE inhibitors, but captopril, enalapril, and lisinopril are inexpensive generics that are absorbed within 30 to 90 minutes, providing BP reduction for 8 hours for the former and 24 hours for the latter two. Few side effects are associated with these drugs if their dose is reduced in renal insufficiency and if they are not given to profoundly volume-depleted patients. Hyperkalemia may be seen in patients with renal artery stenosis and those receiving potassium supplements or nonsteroidal anti-inflammatory drugs. For patients who cannot tolerate ACE inhibitors, angiotensin receptor blockers (ARBs) offer a similar mechanism of action albeit at higher cost.

The parenteral preparation, enalaprilat, is an active form of enalapril that produces rapid (within 15 minutes) BP reduction by inhibiting angiotensin II formation. Initial doses of 1.25 mg IV every 6 hours are usually effective; however, higher doses (up to 5 mg every 6 hours) may be necessary. Enalaprilat may produce severe hypotension in volume-depleted patients. Equally potent hypotensive effects are observed at almost all doses; increasing the dose only extends the duration of action. A long duration of action (nearly 24 hours) represents a
potential disadvantage in cases of overshoot hypotension. ACE inhibitors should not be given in pregnancy. These agents also have the potential to cause acute renal insufficiency and hyperkalemia in patients with circulatory decompensation or when mean arterial pressure is insufficient to support renal perfusion.

**Uncommonly Used Agents**

Hydralazine, a direct vasodilator, is used frequently in stable patients but not in those requiring urgent intervention. Action begins acting within 10 minutes if given IV and within 30 minutes if given intramuscularly. Unfortunately, however, its prolonged duration of action (up to 12 hours) may cause persistent overshoot hypotension. Because hydralazine is not consistently effective at lowering BP or easily reversible when it does, it is a poor choice for acute treatment of life-threatening hypertension. Unless counteracted by a β-blocker, the arteriolar dilating effects of hydralazine often result in reflex tachycardia and enhanced contractility, thereby worsening coronary ischemia and aortic dissection. By reducing its clearance from the body, renal failure potentiates the effects of hydralazine. Hydralazine is generally not an acceptable primary therapy for management of either hypertensive emergencies or urgencies. It may be suitable as an adjunct therapy or as a relatively safe agent for pregnant patients. Hydralazine does reduce uteroplacental blood flow.

Phentolamine is an α-adrenergic blocking drug with an abrupt onset of action (1 to 2 minutes). Its twin effects of α-blockade and non-α-mediated vasodilation precipitate hypotension, tachycardia, nausea, and vomiting in a large percentage of patients who receive it. Unfortunately, reflex tachycardia induced by phentolamine may worsen coronary ischemia, even when beneficial reductions in afterload are achieved. Again, because of the current availability of equally effective and less toxic therapies, phentolamine use has largely fallen out of favor. Repeated boluses of 1 to 5 mg IV to a maximum dose of 15 mg provide control.

**SUGGESTED READINGS**


• Key Points

1. Because venous thromboembolism is so common and in large part preventable, essentially all hospitalized adults with risk factors should be strongly considered for prophylaxis.

2. Owing to its safety, availability, and diagnostic power, ultrasound is the best first diagnostic test when extremity venous thromboembolism is seriously considered.

3. Pulmonary emboli are often difficult to diagnose purely on clinical grounds. Chest imaging studies should be undertaken when suspicion is high and alternative causes are not clearly evident.

4. Most ventilation perfusion scans are nondiagnostic and require either a CT angiogram showing pulmonary embolism or leg study showing deep venous thrombosis for confirmation. A normal ventilation-perfusion scan or a high-probability scan usually suffices for clinical decision-making. A contrast spiral CT scan set for pulmonary angiography is the current gold standard exam.

5. Full-dose anticoagulation with some form of heparin or fondaparinux should be started empirically for almost all patients suspected of having venous thromboembolism, unless bleeding risk is prohibitive.

6. The risk of pulmonary embolism recurrence is in part a function of the duration of time without effective treatment; therefore, early and aggressive anticoagulation is indicated.

7. Removable IVC filters may be an indicated adjunct in patients for whom full anticoagulation presents prohibitive risk.

8. Either weight-based subcutaneous low molecular weight heparin or fondaparinux or IV unfractionated heparin is adjusted every 4 to 6 hours until the activated partial thromboplastin time is in the therapeutic range.

9. There is a much less certain relationship between a high activated partial thromboplastin time and bleeding than there is between a low activated partial thromboplastin time and thrombosis.

10. Thrombolytic or surgical therapy is rarely needed for venous thromboembolism.

MECHANISMS

Pulmonary embolism (PE) results when any insoluble substance gains access to the systemic veins. A contrast CT scan with a large pulmonary embolus is shown in Figure 23-1. Because blood filtering is a natural consequence of the lung’s architecture for optimized gas exchange, small and asymptomatic emboli occur periodically, even in healthy persons. Distinctive syndromes have been described for embolism of air, fat, tumor cells, amniotic fluid, and foreign matter, as well as for bland and infected clots. In critical care, air, fat, amniotic fluid, and septic and bland thrombotic emboli are the major syndromes of interest. Air embolism is discussed in Chapter 8.

Fat embolism, almost always results from trauma or surgery to long bones and pelvis; rarely, vertebral fractures are to blame. Fat emboli do not substantially impede blood flow. Instead, symptoms develop because fatty acid products of lipid digestion produce bronchoconstriction, vasoconstriction, and vascular injury with capillary leak and pulmonary edema (acute respiratory distress syndrome [ARDS]) (see Chapter 24).

Amniotic fluid embolism is a peripartum condition in which amniotic fluid enters the pulmonary circuit. This
syndrome is both inflammatory and obstructive and often presents dramatically with the abrupt dyspnea and pulmonary edema, followed by sudden cardiovascular collapse. The classical risk factors of premature rupture of membranes, older maternal age, and fetal death have been questioned in recent studies. Disseminated intravascular coagulation (DIC) is common among survivors of the initial crisis. Therapy is supportive along with timely delivery of the child.

FIGURE 23-1. Contrast CT scan of the chest with a large embolus at the major branches of the pulmonary artery (arrow).

The major threat to life in septic embolism is not vascular obstruction but septic physiology. Small, friable fragments of infected material embolize to cause fever, toxicity, and a characteristic radiograph: multiple ill-defined infiltrates or nodules (especially lower lobe) of varied sizes frequently cavitate and usually display soft, irregular outlines. Pelvic veins, central venous catheters, right-sided heart valves, and nonsterile injections (related to drug abuse) are common sources of infected material. After identification, the source must be isolated and removed if feasible while the infection is treated vigorously with antibiotics directed at the offending organism(s).

The remainder of this chapter will focus on classical venous thromboembolism (VTE), one of the most frequent and preventable causes of death in hospitalized patients. The term VTE will be used collectively for deep venous thrombosis (DVT) and PE because the link between the conditions is strong. An analogy to cancer treatment can
be made in which DVT represents the primary tumor and PE the metastases. In this comparison, preventing the primary problem negates spread of the disease. Also in line with the cancer analogy, discovering either the primary tumor (DVT) or metastases (PE) mandates treatment and in most cases finding metastases make a search for the primary superfluous. Similarly, on occasion, no primary can be found despite clear metastatic disease. Finally, both VTE and neoplasia are treated with systemic “chemo” therapy; in the case of VTE, it is anticoagulation.

**DEEP VENOUS THROMBOSIS**

**Risk Factors**

In the United States, each year, more than five million patients develop DVT with more than 10% of these patients experiencing symptomatic PE. It is estimated that as many as 250,000 deaths annually can be attributed to such clots. VTE rarely occurs among healthy ambulatory people. Essentially, all victims have easily identified risk factors falling into one of three general categories: stasis of venous blood, injury to the venous intima, and/or hypercoagulability. Thus, increasing age, genetic predisposition, reduced mobility, pregnancy, previous DVT, trauma (especially to the legs), surgery, severe sepsis, cancer, indwelling venous catheters, chronic obstructive pulmonary disease, and heart failure are common predisposing conditions. The more risk factors present, the higher the likelihood of VTE. In the critically ill patient, risks of VTE range from 5% to 25%. Likelihood of VTE can be stratified for certain patient groups undergoing operation. For example, with major orthopedic surgery, 30-day risk of symptomatic VTE approximates 5% without prophylaxis. For patients undergoing abdominal and pelvic surgery, low-risk patients have a 1.5% incidence of VTE, whereas moderate-risk patients have a three percent risk and high-risk patients have a six percent risk of VTE. Extensive pelvic dissection and cancer present increased hazard. There are less data available for other surgical populations. Limited data for craniotomy indicate a risk of VTE as high as 20% when the cause of operation is metastatic disease. Among all craniotomy patients, 30-day risk approximates 4%. Finally, in medical patients, common predisposition to VTE includes active cancer, reduced mobility, cardiovascular disease, obesity, and previous VTE. Prevalence data for VTE in various patient groups is shown in Figure 23-2. Highly predisposed medical patients have a risk of VTE of approximately 10%.

Great interest exists in the half a dozen or so thrombophilic (procoagulant) disorders (e.g., factor V Leiden, prothrombin 20210 mutation, anticardiolipin antibodies, homocystinuria or deficiencies of antithrombin, or proteins C or S). Together, the two most common factor V Leiden (activated protein C resistance) and the prothrombin 20210 mutation can be identified in 5% to 10% of the white population. Despite their high prevalence, VTE risk among those affected remains low in the absence of additional risk factors. Controversy exists regarding the importance of diagnosing thrombophilia, particularly in asymptomatic individuals, and the optimal course of action if diagnosed. Traditional teaching encourages a search for thrombophilia in patients who develop VTE in the absence of other risk factors, especially if young, or when history shows a personal or family history of recurrent thrombosis. Because testing is complex, is expensive, and holds lifelong implications for the patient labeled with an “incurable” genetic disease and their family, evaluation and recommendation should almost certainly be left to a coagulation specialist probably in conjunction with a genetic counselor. Fortunately, there is never an urgency to evaluate patients for these conditions, and their diagnosis does not change the acute VTE treatment. At this time, routine screening of patients with VTE for thrombophilia is not indicated (see Chapter 30).
Clot Sources

Traditional teaching holds that near 90% of PEs result from lower extremity DVTs and that the arms and neck are rarely a clot source. However, changes in practice have altered the epidemiology of the disease; now, hospitalized patients routinely have upper extremity sources of clot. For example, central venous catheters (including peripherally inserted central lines, PICCs) are more common and provide a nidus for thrombus formation. Embolization is possible upon catheter removal, as the encasing thrombus is stripped away. It is now estimated that central catheters elevate the risk of PE perhaps as much as 10-fold. In contrast to disease of the deep veins, superficial thrombophlebitis manifest by erythema, tenderness, and a palpable “venous cord” poses a lower VTE risk and can usually be treated symptomatically. On rare occasions, ultrasound reveals extension into the deep veins and higher risk for embolism.

The natural history of leg DVT is well characterized. Most clots begin as asymptomatic calf thrombi. Unfortunately, 30% to 50% of these bland clots propagate above the knee and 30% to 50% of proximal DVTs eventually produce PE. Therefore, between 10% and 25% of untreated patients with calf thrombi develop PE. Surprising to many clinicians is the fact that during life, most acute thrombi in the legs and lungs are asymptomatic and, therefore, go undiagnosed.
Prevention

Prevention is the most important treatment of VTE. In fact, deterrence is so important and so often overlooked that it makes sense to institute hospital-wide prophylaxis programs for patients at risk. Fortunately, nearly 90% of ICU patients in the United States now receive some form of effective prophylaxis. However, rates of protection are profoundly less for lower-risk (but still VTE predisposed) patients treated in hospital outside the ICU.

DVT risk seems likely to be reduced by early mobilization. A corollary is that avoidance of excessive sedation and unnecessary paralysis could reduce risk by shortening periods of immobility. Unfortunately, mobilization is ordered for hospitalized patients more often than performed, and activity never reaches normal levels. Even if frequent and vigorous walking were undertaken, doing so would reverse only one of the numerous VTE risk factors present in most hospitalized patients.

Because of its superior effectiveness, pharmacologic prophylaxis should be provided to inpatients with VTE risk factors unless there is a contraindication to use. Decision support tools are available to support VTE prophylaxis in high-risk patients (Table 23-1).

Fixed-dose subcutaneous (SC) unfractionated heparin (UFH) reduces DVT risk by as much as 66% in general medical and surgical patients when given thrice daily. Unfortunately, higher-risk patients (i.e., critically ill, multitrauma, hip or knee replacement, or intraabdominal or pelvic cancer surgery) do not enjoy the same protection. Those at highest risk should receive an appropriate dose of a low molecular weight heparin (LMWH) or fondaparinux, UFH in a dose adjusted to prolong the activated partial thromboplastin time (aPTT) (typically 7,500 to 10,000 units SC every 8 hours), or oral warfarin given in a dose and over a duration sufficient to prolong the prothrombin time (PT). When used in fixed prophylactic doses, UFH and LMWH do not prolong the aPTT or increase serious hemorrhagic complications; however, all heparins and fondaparinux tend to accumulate when glomerular filtration rate (GFR) falls below 30 mL/min, increasing the likelihood of bleeding (see Chapter 30).

Table 23-1. Decision Support Tool for Venous Thromboembolism Prophylaxis

<table>
<thead>
<tr>
<th>Thrombosis Risk Factor Assessment (Choose all that apply):</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Point</td>
</tr>
<tr>
<td>Age 41-60 y</td>
</tr>
<tr>
<td>Minor surgery</td>
</tr>
<tr>
<td>BMI 25 kg/m² or greater</td>
</tr>
<tr>
<td>Swollen legs</td>
</tr>
<tr>
<td>Risk Factor</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Surgery lasting longer than 45 min</td>
</tr>
<tr>
<td>Pregnancy or post-partum</td>
</tr>
<tr>
<td>History of unexplained or recurrent abortion</td>
</tr>
<tr>
<td>Oral contraceptives or hormone replacement</td>
</tr>
<tr>
<td>Oral contraceptives or hormone replacement</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Serious lung disease including pneumonia</td>
</tr>
<tr>
<td>Abnormal pulmonary function</td>
</tr>
<tr>
<td>Acute Myocardial Infarction (AMI)</td>
</tr>
<tr>
<td>Congestive Heart Failure (CHF)</td>
</tr>
<tr>
<td>History of inflammatory bowel disease</td>
</tr>
<tr>
<td>Medical patient at bed rest</td>
</tr>
</tbody>
</table>

**Level of Risk Categorization**

**NOTE:** *For patients with increased risk of bleeding, sequential compression devices (SCDs) alone may be appropriate*
<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>Total Risk Factor Score</th>
<th>Incidence of DVT</th>
<th>Prophylaxis Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW Risk</td>
<td>0-1</td>
<td>2%</td>
<td>Early ambulation</td>
</tr>
<tr>
<td>HIGH Risk</td>
<td>2</td>
<td>10%-20%</td>
<td>Order pharmacologic and mechanical prophylaxis unless contraindicated</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>20%-40%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 or more</td>
<td>40%-80%</td>
<td></td>
</tr>
</tbody>
</table>


LMWHs equal or surpass the effectiveness of UFH for VTE prophylaxis and have lower incidence of bleeding and heparin-induced thrombocytopenia (HIT). Overall, LMWHs provide greater than 75% relative risk reduction for DVT formation. High bioavailability (approx. 90%) and longer half-life allow single daily injections for many indications. Because each LMWH has different pharmacological properties and few head-to-head comparisons have been conducted, LMWHs should not be considered interchangeable. There is little financial incentive to choose one over another, as differences in cost among brands is trivial. To avoid confusion regarding dose and frequency and to control costs, it makes sense to limit the number of prophylactic agents on the formulary. As a result, many institutions select one LMWH for a broad range of indications. The higher costs of LMWHs compared to UFH for prophylaxis seems well worth the investment, given the superior effectiveness, lower incidence of HIT, and reduced number of injections required. The price differential has also dramatically narrowed in recent years.

For patients undergoing major orthopedic reconstructive surgery (hip or knee replacement or hip fracture stabilization), LMWH prophylaxis is effective if started 12 hours prior to operation and resumed 12 hours after operation. Fondaparinux is a synthetic factor Xa inhibitor, which has been shown to be an effective prophylaxis for patients undergoing abdominal, knee, and hip surgery. High bioavailability is advantageous but lack of reversibility, dependence on renal clearance, and the extremely long half-life are disadvantages. Fondaparinux should not be used in patients with renal insufficiency. Studies comparing this drug to LMWH demonstrate a slightly lower DVT risk (with a low overall clot risk for both agents) and a comparable risk of PE. There does not appear to be an advantage of fondaparinux over an appropriately selected LMWH. Bivalirudin, another factor Xa inhibitor, may be considered when heparins are contraindicated because of the presence of HIT. Unfortunately, because there is no product that reverses its action, utility of this agent in titration of therapy is limited. A typical dose is 0.15 to 0.2 mg/kg/h given intravenously and adjusted to aPTT 1.5 to 2.5 times the baseline value.

Dextran, aspirin, and other nonsteroidal antiinflammatory drugs (NSAIDs) and dipyridamole should be avoided because they have not been shown to be as effective as UFH, LMWH, fondaparinux, or warfarin prophylaxis and may impose adverse side effects, such as renal insufficiency and gastrointestinal bleeding. Custom-fitted, elastic, graded compression stockings and pneumatic compression devices (such as foot pumps) are options for patients at unacceptable risk for bleeding if given anticoagulants (e.g., coagulopathy, trauma, or neurosurgery). Interestingly, the mechanism of action of these mechanical devices is probably not the mere squeezing of blood from the legs, but in part an antithrombotic and profibrinolytic effect induced by vascular endothelial compression. Alone, each device has been shown to reduce the risk of DVT, with even lower rates observed when they are used concurrently. At a 30% relative risk reduction...
for custom-fitted elastic stockings and a 50% relative risk reduction for pneumatic compression devices, neither is as effective as pharmacologic prophylaxis. Because of patient discomfort or through sheer forgetfulness, these devices are often not worn at all or are applied inconsistently. Furthermore, elastic stockings often fit poorly because they are rarely custom manufactured. Obviously, if malfitting or not worn, neither device offers protection. In addition, the effectiveness of lower extremity mechanical devices to reduce the risk of upper extremity (often catheter related) DVT is questionable.

**Diagnosis**

The signs of DVT relate to venous inflammation and obstruction. Unilateral lower extremity erythema, warmth, swelling, edema, and pain suggest DVT. The Homans sign is a nonspecific indicator of calf inflammation and is frequently not present in documented DVT. Unfortunately, the physical examination is poor for detecting DVT and distinguishing it from common mimics.

Several common conditions resemble DVT. A ruptured Baker cyst presents as a mass in the calf with pain and erythema, usually in patients with rheumatoid arthritis. An accurate diagnosis must be made to avoid the use of potentially dangerous therapies (e.g., anticoagulants) that could provoke bleeding into the cyst. Rupture of the plantaris tendon also may mimic DVT on examination, but the history is key, revealing recent exertion with the acute onset of pain. Crystalline arthritis (gout or pseudogout) may produce intense joint space inflammation that extends into the calf. Cellulitis, especially that seen in the setting of direct trauma or chronic fungal infection of the feet or after coronary bypass surgery, often is confused with DVT. It is frequently so difficult to distinguish DVT from cellulitis that concomitant antibiotic and anticoagulation therapy are begun empirically until DVT is confirmed or excluded. Although sometimes confused with DVT, osteoarthropathy presents with pain, tenderness, and swelling over the anterior tibia, with or without clubbing, and can be confirmed radiographically. In patients with hemophilia or those taking anticoagulants, hematoma formation in the calf muscles also may produce a syndrome clinically similar to DVT. Postphlebitic syndrome (deep venous insufficiency) develops to some degree in nearly half of all patients after a DVT. The syndrome, which typically becomes fully manifest over 3 to 5 years, can be a particularly confounding problem because the recurrent discomfort and swelling that occurs often prompts frequent DVT reevaluations.

**Diagnostic Testing**

Because the physical examination is insensitive and nonspecific, a confirmatory study is necessary in essentially all cases. Although immensely popular, the D-dimer is of little or no diagnostic value in hospitalized patients because its concentration is increased by essentially every critical illness (e.g., stroke, severe sepsis, trauma, surgery, pregnancy, liver failure, myocardial infarction). This differs from the outpatient setting where a negative D-dimer is common, and when a negative result is paired with a low validated risk score (e.g., Wells criteria), the likelihood of clot is so small no additional testing is indicated.

Ultrasound (US) is capable of imaging veins and probing venous flow. When noncompressible clot is imaged, the diagnosis is all but certain. Doppler studies can reliably confirm obstruction, unless flow is compromised by locally restricted arterial supply, reduced cardiac output, or high intra-abdominal or central venous back pressures. In such cases, low venous flow may be reported but clot may not be seen. US is not as sensitive as contrast venography for detecting calf clot and may miss some clots restricted to the pelvis. Portability, low cost, and unquestioned safety make US the preferred first test in the ICU population despite its limitations.
The contrast venogram is simultaneously the most sensitive, definitive, time-consuming, and potentially injurious method for detecting DVT. An advantage to venography is its ability to visualize thrombus from the feet to the vena cava. Venography also occasionally helps distinguish acute thrombosis from chronic thrombosis based on appearance of the clot and is immune to false-positive results brought about by low flow states. Because radiocontrast agents may precipitate renal insufficiency and cause allergic reactions and phlebitis, venography is infrequently employed today.

In up to one third of cases of angiographically proven PE, studies for DVT are negative. This situation could be because all leg clots have embolized to the lung or the legs were not the source of the PE. Although a negative leg US or venogram does not exclude a diagnosis of PE, in almost all cases, a positive study permits VTE treatment to be initiated without additional testing.

**PULMONARY EMBOLISM**

**Natural History**

Because PE is a consequence of its root disease, prophylaxis for DVT decreases PE rates. Between 30% and 50% of patients with proximal DVT can be shown to have a PE, even though the vast majority have no attributable respiratory symptoms. Tragically, the very first symptom of PE in the hospitalized patient is often sudden cardiovascular collapse. When symptoms lead to a diagnosis of PE during life and effective treatment is begun, the outcome is generally good, with mortality rates less than 10%. Subgroups at highest risk for death include patients with shock and refractory hypoxemia. The utility of echocardiography and biochemical testing (e.g., troponin, creatine phosphokinase, or natriuretic peptides) to identify higher-risk patients remains unproven.

**Symptoms and Signs**

Signs and symptoms of PE are modified in severity and duration by underlying cardiopulmonary status. No symptom or physical finding is either universal or specific. Therefore, when PE is suspected, the patient should be anticoagulated empirically until the diagnosis of VTE is refuted or confirmed by objective testing. (The obvious exception would be patients who are hemorrhaging or at very high risk to bleed.) For most patients, the symptoms of PE spontaneously improve within the first few hours or days after the event. Signs disappear more slowly. Among conscious patients with large emboli, the following signs and symptoms are observed: dyspnea and tachypnea (90%); pleuritic pain (70%); apprehension, rales, and cough (50%); and hemoptysis (30%). Tachycardia (>100/min) and fever occur in a significant minority of cases. Syncope is the result of massive embolism. It is important to note that for sedated, mechanically ventilated patients, the only clues to the disease may be worsening of baseline tachycardia and an increase in minute ventilation.

Pulmonary artery pressures do not rise markedly unless the embolism obstructs a significant portion of the capillary bed or the circulation was previously compromised. Therefore, a right-sided gallop, increased pulmonic component of the second heart sound (P₂), or pulmonary hypertension documented by echocardiography or pulmonary artery catheterization signify either massive acute obstruction or lesser obstruction in a patient with underlying pulmonary vascular disease. Detection of a pleural effusion may be helpful: among patients with pleuritic chest pain, PE is a more likely diagnosis than infection when effusion is present.

**Routine Diagnostic Tests**

Routine diagnostic tests (chest X-ray [CXR], electrocardiogram [ECG], blood gases, leukocyte count) are most useful to exclude alternative diagnoses (e.g., pneumonia, pneumothorax, myocardial infarction, and pulmonary edema) rather than to confirm a diagnosis of PE.
**Electrocardiogram**

The ECG is sensitive but nonspecific. Even in patients without prior cardiopulmonary disease, the ECG remains completely normal in only a small proportion (approx. 10% to 15%). Nonspecific ST and/or T wave changes occur in most patients. Except for moderate sinus tachycardia, rhythm disturbances are unusual. Atrial fibrillation and flutter seldom occur in patients without pre-existing cardiovascular compromise. Similarly, bundle-branch block is highly unusual but when it occurs, left and right tracts are affected equally often. ECG evidence of acute cor pulmonale (S₁, Q₃, or T₃ pattern or acute right bundle-branch block) is occasionally encountered (<10%) and when detected suggests severe vascular obstruction.

**Blood Studies**

Although hypoxemia is often discussed, emboli frequently are found in patients with normal values for PaO₂, PaCO₂, and A-a gradient. Arterial blood gas (ABG) values within the normal range do not exclude the diagnosis of PE; young, otherwise healthy patients have normal results up to 40% of the time. Although seldom measured, dead space fraction and VE/PaCO₂ ratio are more reliably high after PE. As a general rule, the more profound the underlying cardiovascular disease, the less likely the ABG is to be normal when a PE occurs.

Fibrin degradation product assays (e.g., D-dimer) are not usually helpful in hospitalized patients. Although a negative sensitive D-dimer assay can be helpful in refuting a VTE diagnosis in low-risk outpatients, the test is almost uniformly positive in inpatients, which limits its utility. (Severe sepsis, renal failure, surgery, pregnancy, and trauma all increase the D-dimer levels even in the absence of clot.) It is important to know which d-dimer test is used in a given institution; several assays are available, some of which have dismal sensitivity and specificity. It is not prudent to bet an inpatient's life on a negative D-dimer (or any other single study) without confirmatory clinical, radiographic, or laboratory data.

**Chest Radiograph**

Nonspecific findings, including cardiomegaly, pleural effusion, hemidiaphragm elevation, consolidation, and atelectasis, are common. Indeed, the CXR remains unchanged from the pre-event film in less than one quarter of all patients. Small or moderately sized effusions occur in approximately one fourth of all cases; most (but not all) are exudative. Embolic effusions tend to appear early and unilaterally. A bloody effusion found before anticoagulation suggests infarction or an alternative diagnosis (e.g., tuberculosis, malignancy, trauma). More specific features, including segmental oligemia (the Westermark sign) and Hampton hump (a wedge-shaped peripheral density resulting from pulmonary infarction), are unusual. Infiltrate may represent parenchymal hemorrhage (resolving rapidly without effusion) or infarction (resolving slowly, often accompanied by a bloody effusion). Fresh infarcts nearly always are pleural based and cavitate frequently. Because the dual parenchymal blood supply usually protects against tissue ischemia, infarction occurs most commonly in patients with pre-existing cardiopulmonary disease. When resolving, the infiltrate often rounds up to form a spheroid “nodule.” Multiple, widely scattered, cavitating infiltrates that develop acutely suggest septic emboli.

**Specialized Diagnostic Tests**

Clinical judgment plays an indispensable role in the diagnosis of PE. Chest CT angiography is now the gold standard for making the diagnosis of PE when renal function permits it to be performed. Because contrast CTs are noninvasive and are perceived to offer little risk, there is often a low threshold to order them for patients with dyspnea or chest pain. However, these studies are expensive, expose patients to radiation, and have the added risk of contrast exposure. Casual ordering frequently creates a dilemma when the result of a CT scan is at odds with the clinical situation. A consultant is then summoned to explain the results. Such patients are often
unnecessarily subjected to additional testing or anticoagulation with an uncertain diagnosis. The best strategy is not to perform a CT scan unless (1) the clinical likelihood of PE is significant and (2) there is a commitment to pursue the diagnosis to certainty or exclusion should the scan prove inconclusive.

**Ventilation-Perfusion Scans**

The role for these studies has been diminished by the improved quality of current chest CT angiography. However, they are a key “fall-back” alternative when the radiocontrasted CT is contraindicated. A perfusion (Q) scan is performed by injecting radioactive macroaggregated albumin, a compound with a particle size exceeding the diameter of the alveolar capillary. The albumin is then trapped in perfused lung areas. Areas devoid of perfusion are suspect for PE but also can result from tumor, obstructive lung disease, tissue compression, or hypoxic vasoconstriction induced by airspace disease. Therefore, atelectasis, emphysema, ARDS, and pneumonia all can induce perfusion defects. In an attempt to exclude airspace disease as a cause of a perfusion defect, a CXR is performed routinely. Because infiltrates can change rapidly in hospitalized patients, the comparison CXR should be obtained within hours of the scan. The diagnosis of PE is more likely when the perfusion scan defect occurs in an area without apparent disease on CXR.

To further increase the specificity of the perfusion scan, a ventilation (V) scan can be added on occasion to the diagnostic package. A major limitation to doing so for the ICU patient is the inability to obtain the ventilation portion of the study in those mechanically ventilated. When performed, the ventilation scan is used to identify poorly ventilated areas that could cause regional reductions in perfusion. When a large perfusion defect occurs in a normal area on plain CXR that also is normally ventilated on VQ scan, PE is likely. The ventilation scan (xenon or diethylenetriamine penta-acetic acid) improves specificity for embolism; gross regional VQ mismatching often allows a diagnosis to be made with confidence. However, matching VQ abnormalities sometimes occur in PE because of bronchoconstriction, atelectasis, or secretion retention. Conversely, mismatching can occur when no embolus is present.

Criteria for “high-probability” and “low-probability” scans vary with the interpreter but generally depend on the size, number, and distribution of perfusion defects, as well as their relationship to CXR and ventilation scan abnormalities. A perfusion defect larger than a corresponding density on chest film suggests embolism; a perfusion defect equal to or smaller than the radiographic abnormality suggests that embolism is less likely. A similar rule applies even more strongly to areas of VQ mismatching. Experts often disagree among themselves in interpretation of VQ scans; consequently, the false-positive rate may be very high in some centers. Classically, scans are interpreted as falling into one of four categories: (1) normal, (2) low probability, (3) intermediate probability, and (4) high probability. However, a more practical scheme is to classify scans as only normal, high probability, or indeterminate.

The most useful of all scans, a perfectly normal perfusion study, effectively rules out a clinically significant PE. The single rare exception to this rule may be submassive PE confined to the pulmonary outflow tract, producing symmetric reduction in flow as a result of central obstruction. (Contrast CT scans easily detect such clots.) The second most useful VQ result is the finding of multiple mismatched VQ defects of segmental or greater size. Such a result in a patient with a high clinical probability is associated with at least a 90% likelihood of a PE.

Unfortunately, most scans (nearly 70%) are interpreted as low or intermediate probability (i.e., indeterminate), which is unhelpful. A low-probability or indeterminate scan should not be confused with a normal scan. A substantial fraction (up to 15%) of patients with low-probability scans (matched subsegmental defects) have demonstrable PE. Similarly, up to 50% of patients with indeterminate scans (matched or mismatched segmental defects) have PE. Therefore, a low-probability or indeterminate scan almost always requires additional diagnostic testing if the clinical suspicion of PE is high.
The problem of a false-positive scan is common for the ICU patient in whom the prevalence of underlying cardiopulmonary disease is high. In general, perfusion defects in patients with proven PE are multiple and bilateral. Hence, the diagnosis of PE should be suspect when abnormalities are single or unilateral. Complete unilateral absence of perfusion with a normal contralateral lung probably is more likely to be the result of a mediastinal tumor, central mucous plug, bronchial cyst, or congenital pulmonary artery defect than PE. Emboli isolated to the upper lobes are unusual in ambulatory patients whose blood flow, when upright, distributes preferentially to the bases—this rule is often violated in bedridden patients in the ICU.

**Contrast CT Scanning**

The contrast helical CT scan, often called a "spiral CT," has become the most popular diagnostic test, in large part because improved resolution and rapid image collection with current systems. When ordering a CT scan for suspected PE, it is important to communicate that fact to the radiology staff so that optimal technique is used. The speed with which the scan is obtained (largely determined by the number of rows of detectors); the direction of scanning (foot to head or vice versa); the amount of contrast, infusion rate of contrast, and gating of contrast; width of the CT slice; and the reconstruction method all impact ability to detect emboli. Another factor contributing to the popularity of CT is the apparent simplicity of interpretation compared to the VQ scan. This is translated into the common but exaggerated belief that there is never uncertainty and CT scans are only “positive” or “negative.” In a large trial evaluating the diagnostic accuracy of CT imaging, specificity for CT angiography was 96% with sensitivity 83%. If venous imaging is included, sensitivity increases to 90% with CT angiography. Positive predictive value of CT angiography depends on the location of embolism. Positive predictive value is 97% for involvement of main and lobar arteries and 68% for segmental disease and 25% for subsegmental disease. Application of clinical information improves positive and negative prediction values. CT angiography in high-risk patients has a positive predictive value of 92%, whereas in low-risk patients, the negative predictive value is 96%. CT scans may be indeterminate because of morbid obesity, motion artifact, or suboptimal contrast technique. The perceived simplicity in reading CT can be seductive; the inexpert reader may interpret “streaming artifact” from poor contrast injection technique and image timing or low cardiac output as PE. Likewise, false-positive CTs can result from pulmonary artery compression from mediastinal lymphadenopathy, fibrosis, or tumor. Nevertheless, when a technically adequate CT demonstrates one or more luminal filling defects, especially if bilateral, PE is near certain. By contrast, a “negative CT” does not mean absence of PE; clot at the subsegmental level and beyond is often missed, as is chronic thromboembolic disease.

CT has some clear disadvantages. In all cases, contrast is needed, making the CT less attractive than perfusion scanning in patients at risk for kidney injury. There is also a growing awareness of the dangers of diagnostic radiation from repeated CT. Newer-generation scanners, however, reduce radiation exposure. Another drawback of the CT is the need to breath-hold during the scanning—a difficult task for the dyspneic patient. Failure to remain motionless can result in false-negative studies.

**Echocardiography**

Transthoracic and transesophageal echocardiography are sometimes diagnostic and are both useful adjuncts in the care of patients with PE. For example, in an ICU patient who develops unexplained hypotension, an echocardiogram showing new right ventricular (RV) dilation and hypokinesis, and tricuspid regurgitation, with normal left ventricular (LV) function is suggestive of acute PE. Suspicion of PE is confirmed when on rare occasion, clot is visualized in the right heart or pulmonary outflow tract, the so-called clot in transit. Alternatively, that same study could reveal non-PE causes of hypotension: a large pericardial effusion, isolated poor LV contractility suggesting ischemia or infarction, or normal ventricular contractility and inspiratory vena cava collapse suggesting intravascular volume depletion. Other findings supporting, but not diagnostic, for
PE include loss of respiratory variation in inferior vena cava (IVC) diameter and intraventricular septum bulge into the LV. Clinically significant PE may also occur in the absence of any abnormal RV findings on echocardiography. Although study continues, at this time, echocardiographic findings do not appear to carry sufficient weight to dictate the type of treatment. Specifically, RV dilation is so common a finding in patients with nonhemodynamically significant PE that it does not in itself mandate thrombolytic therapy nor surgical or radiological intervention.

**Angiography**

Pulmonary angiography is the old gold standard for identifying PE. If formal angiography is performed, measurements of intracardiac and pulmonary artery pressures and cardiac output may be obtained. Such measurements may confirm alternate diagnoses (e.g., primary pulmonary hypertension, mitral stenosis) if the angiogram fails to show PE. Criteria for an angiographic diagnosis must include an intraluminal filling defect or an abrupt convex “cutoff.” (Oligemia and vessel tortuosity are nondiagnostic.) In the absence of DVT, a negative angiogram, carefully performed within 48 hours of the onset of symptoms, indicates a negligible risk of clinically significant PE. Angiograms performed without “cut films,” selective injections, multiple views, and magnification may miss small emboli.

Risks of arteriography have been greatly overstated—the overall mortality rate is lower than 0.01%. Likewise, there is a low risk of allergic dye reaction and vascular damage (right ventricular or pulmonary artery perforation). Catheter-induced arrhythmias usually are self-limited or easily treated. The greatest risks are incurred during contrast injection in patients with severe pulmonary hypertension, but even then, patients can safely undergo selective angiography with nonionic contrast media. If subsequent thrombolytic therapy is contemplated, punctures of noncompressible vessels should be avoided.

**VTE Diagnostic Plan**

No universally applicable diagnostic protocol can be recommended; however, one rational strategy is suggested in [Figure 23-3](#) and explained below. Usually, the best first diagnostic test is bilateral lower extremity US. If positive, the need for anticoagulation is established, and information is provided as to the extent of clot and potential for subsequent PE. A negative study makes placement of an IVC filter superfluous, even if PE is present because there is no “at-risk” thrombus. Although lower extremity US will be negative in many cases of PE, safety, low cost, and portability make it an excellent first choice.

In healthy males over the age of 18, CT angiography is the defining second study for PE. CT angiography should not be performed if GFR is 35 or less. Patients with a low GFR and/or severe contrast allergy should undergo chest X-ray with nuclear perfusion scanning instead. Ventilation scanning may be considered to check correspondence of defects identified with findings on chest X-ray. In women under 40, and particularly for pregnant patients, venous ultrasound is the initial study of choice for lower extremity symptoms and to evaluate for PE. Secondary studies include chest X-ray and perfusion scanning, which may be obtained if chest X-ray is normal. CT angiography is avoided in these female patients because of radiation exposure even with newer-generation machines. Women over 40 may receive CT angiography to evaluate for pulmonary emboli in the absence of significant contrast allergy or poor renal function. As above, chest X-ray and perfusion scanning are considered in patients with poor renal function or significant contrast allergy. Pulmonary arteriography is rarely performed. Because the therapy of DVT and PE usually is identical, demonstrating a DVT obviates the need for additional chest imaging. Given all these considerations, an angiogram should be considered (1) when thrombolytic therapy or interventional radiology or surgical embolectomy is contemplated, (2) when paradoxical embolism is suspected (to document right-to-left shunt or PE), and (3) when there is a high clinical suspicion of PE but leg US is negative and CT scan is nondiagnostic.
Prognosis and Rate of Resolution

A significant percentage of patients with massive PE die before the diagnosis is made, usually within hours of embolization. Adequately anticoagulated patients who survive the initial insult have an excellent prognosis. If effective anticoagulation is not begun, clinically significant PE recurs in at least one third of cases. This risk falls to less than 10% with fully effective anticoagulation. Whether or not VTE is treated, subclinical recurrence of PE (new lung scan defect) occurs in approximately 5% of patients, most within the first several days of initiating therapy. For well-anticoagulated patients, such early episodes represent embolization of preformed thrombus, not additional thrombus proliferation, and thus do not represent “anticoagulation failure.” Because the thrombus is already formed, vena caval filtering may be the only therapy that might lower the incidence of PE.

FIGURE 23-3. Flow diagram of one strategy for evaluating inpatients with suspected PE. CT, computed tomography; CXR, chest X-ray; DVT, deep venous thrombosis; PE, pulmonary embolism; US, ultrasound; VQ, ventilation-perfusion; VTE, venous thromboembolism.
Hemodynamic and gas exchange abnormalities usually reverse rapidly in patients who survive long enough for treatment to be started. Distal migration or shrinkage or fragmentation of clot certainly plays a role in this improvement, but vasoactive mediators (e.g., thromboxane and prostacyclin) are also operative. Imaging findings can improve within 12 to 48 hours but usually require 2 to 3 weeks or longer for complete resolution. Likewise, perfusion scan defects may disappear quickly (over days) but often resolve over weeks to months. Most (approx. 85%) of all perfusion defects resolve within 3 months; defects persisting at that time are likely to be permanent. Prospective studies suggest that chronic thrombotic pulmonary hypertension develops in 3% to 4% of PE victims, although it is not clear if in situ thrombosis, recurrent silent emboli, or clot triggered vascular remodeling is to blame. The problem of chronic thrombotic pulmonary hypertension can be vexing unless the patient is generally healthy and the clot is amenable to thromboendarterectomy.

DVT and PE Treatment

Acute Anticoagulation

The treatments of DVT and PE rarely differ; therefore, making the diagnosis of either usually obviates the need to search for the complementary condition. The goals of treatment are to prevent clot extension, preserve venous architecture, and relieve pain. Because anticoagulation does not dissolve clot, even optimal therapy does not guarantee that PE will not occur in patients with established DVT. Although bed rest may reduce swelling and discomfort in the legs of patients with DVT, the need for bed rest to prevent dislodging clots is disproven. In fact, patients with DVT treated outside the hospital with unrestricted activity have lower rates of embolization than those confined to bed. For patients with DVT, the application of graded compression stockings as soon as possible and continued for 6 to 12 months helps deter development of postthrombotic venous insufficiency. Figures 23-4 and 23-5 describe the types of anticoagulants available and points of action in the clotting cascade.

Drugs Used to Treat Clotting Disorders

- **Anticoagulants**
  - Direct Thrombin Inhibitors
  - Indirect Thrombin Inhibitors
  - Vit K Epoxide Reductase Inhibitor
  - Direct Xa Inhibitors

- **Thrombolytics**
  - Plasminogen Activators

**FIGURE 23-4.** Anticoagulants can be divided into four categories. Direct thrombin inhibitors act by immediate contact with thrombin, whereas the indirect thrombin inhibitors act through antithrombin-3. Ineffectiveness of indirect thrombin inhibitors should trigger measurement of an antithrombin-3 level. Indirect
thrombin inhibitors may also inactivate factor Xa and factor VIIIa. Vitamin K epoxide reductase inhibitors (i.e., warfarin) work through the vitamin K-dependent clotting factors IX, X, prothrombin, and VII. Direct factor Xa inhibitors do not require antithrombin for effect. Thrombolytic agents activate plasminogen yielding plasmin and fibrin strands. Clot-specific fibrinolytic agents produce some degree of systemic fibrinolysis that can deplete circulating fibrinogen and create an increased bleeding risk.

VTE can be treated using weight-based intravenous or SC UFH titrated to aPTT or anti-Xa levels. The use of anti-Xa levels is becoming more popular because of technical complications affecting PTT measurement. At present, however, anti-Xa heparin monitoring is not widely validated by outcome studies. VTE may also be treated by SC LMWHs (enoxaparin or dalteparin), fondaparinux (inhibitor of Factor Xa), warfarin (vitamin K antagonists), or new oral anticoagulants (dabigatran, rivaroxaban, apixaban, or edoxaban). A recent meta-analysis comparing fixed-dose LMWH with UFH or LMWH with UFH administered either as an adjusted dose intravenously or a fixed dose subcutaneously found that LMWH was associated with fewer deaths, less major hemorrhage, and lower rates of VTE. LMWH is effective and easily administered, making it a preferred anticoagulant in both the outpatient or inpatient setting. Direct oral anticoagulants (DOACs) are seeing a growing role in VTE treatment. These agents may be preferred, ultimately, for outpatient VTE management.

FIGURE 23-5. Site of action for anticoagulant agents previously described is indicated on this diagram of the clotting cascade. For additional detail, see Chapter 30.
Unfractionated heparin should be considered for patients with renal insufficiency in the acute setting because LMWH is predominately excreted in the urine. Because its effects can be rapidly and temporarily reversed, UFH is often preferable when surgical or procedural intervention is anticipated in the near future. Key elements of an UFH protocol are as follows: (1) empiric anticoagulation while awaiting a confirmatory diagnostic test unless the patient is bleeding; (2) weight-based dosing with a maximum cutoff for morbidly obese patients; (3) use of an initial 80 to 100 units/kg bolus dose as well as subsequent bolus doses for a subtherapeutic aPTT or anti-Xa level (40 to 50 units/kg or 80 to 100 units/kg); (4) a high-intensity UFH infusion rate (18 to 20 units/kg/h); (5) performing a 6-hour postbolus aPTT or anti-Xa level to prove adequate anticoagulation intensity; and (6) frequent (typically every 6 hours) monitoring until therapeutic aPTT or anti-Xa level is achieved.

Historic reports suggest that approximately 1% of anticoagulated patients will suffer some bleeding complication each day of treatment accounting for overall 10% incidence of hemorrhage during hospital-based LMWH or UFH therapy. More recent data suggests that the risk of major bleeding with UFH is 5% to 10% and LMWH is 4%. Spontaneous hemorrhage is rare in the absence of compromised vascular bed, renal insufficiency, impaired platelet function, or massive UFH overdose. Therefore, bleeding is most common among alcoholics, the elderly, postoperative patients, and patients receiving drugs impairing platelet function. If serious bleeding occurs on UFH, the drug should be stopped and its anticoagulant effect will wane in roughly 8 hours (half-life of UFH is approximately 1.5 hours). Reversal of UFH is accelerated by using protamine sulfate (1 mg protamine for every 100 units of heparin to a maximum dose of 50 mg). If 30 minutes have elapsed since the last dose of heparin, one half of the protamine dose may be sufficient.

Suboptimal because of discomfort to the patient and complexity of monitoring, UFH may also be given subcutaneously if venous access is problematic. A fixed-dose or adjustable weight-based dosing strategy with aPTT monitoring may be employed. One example of a fixed-dose strategy for treatment for VTE is approximately 300 units/kg followed by 250 units/kg every 12 hours.

LMWHs are replacing continuous infusion UFH because of superior efficacy (see above), ease of administration and reduced total cost of therapy. LMWHs are associated with fewer bleeding complications and a lower risk of HIT. The risk of this important complication is 2.6% with UFH and 0.2% with LMWH. Intermittent SC LMWH injections without aPTT monitoring reduce cost and shorten hospital stay. Many reliable patients with DVT with or without PE are now being treated on an outpatient basis if they are hemodynamically stable and do not require oxygen. When serious bleeding develops in a patient receiving therapeutic doses of LMWH, the drug is stopped. Because of longer half-lives, most anticoagulant effect of LMWHs disappears over 12 to 24 hours instead of 8 hours for UFH. In general, therapeutic doses of UFH or LMWH should be continued for 5 days during which a vitamin K antagonist (warfarin) is initiated and continued until the patient is on a therapeutic dose. In contrast, the DOACs (rivaroxaban, apixaban, edoxaban) do not require overlap, and UFH and LMWH may be discontinued when these agents are initiated. Fondaparinux is a rapidly absorbed synthetic factor Xa inhibitor. This agent is another alternative to LMWH and UFH for initial treatment of VTE. Fondaparinux has a long half-life allowing oncedaily weight-based SC doses to be used. Bleeding rate (2% to 3% during VTE treatment) is comparable to UFH and LMWH in recent trials.

In patients with proximal DVT or PE, anticoagulation for 3 months is recommended. Where cancer is not a comorbid condition, DOACs such as dabigatran, rivaroxaban, apixaban, and edoxaban are recommended over the traditional vitamin K antagonist warfarin because of greater ease of use. Where a DOAC is not used, warfarin is recommended over prolonged therapy with LMWH. Where cancer is an associated diagnosis with DVT of the leg or PE, LMWH is recommended over warfarin or DOACs. Where therapy is prolonged beyond 3 months, there is no need to change the treatment strategy used. Compared with
historic long-term treatment involving warfarin, new DOACs are not inferior for recurrent thromboembolism and have similar or fewer major bleeding complications. Direct oral anticoagulants are easily administered and do not require the monitoring needed for chronic warfarin therapy. A reversal agent for dabigatran is now available with others development. Renal insufficiency limits use of these newer anticoagulant agents. Limited available data support the practice of excluding the use of new DOACs in patients with GFR less than 30.

Acute anticoagulation in special populations deserves comment. Caution should be exercised when giving any type of heparin to patients with renal insufficiency (i.e., GFR < 30 mL/min) because all varieties accumulate, enhancing the bleeding risk. In patients with renal insufficiency, bleeding may be more common with LMWH compared to UFH for two reasons: first, UFH is typically monitored with an aPTT and hopefully doses are adjusted downward as the aPTT climbs, whereas in vitro monitoring is not usually performed with LMWHs. Anti-Xa assays can be done, but doing so counters the cost and convenience advantages of LMWHs. Second, the longer half-lives of LMWHs may disproportionately predispose to drug accumulation. Thus, when dialysis-dependent patients require full anticoagulation, for now, it is probably best to use UFH. Because fondaparinux has no antidote, is exclusively cleared by the kidney, and has a half-life of 17 hours even when renal function is normal, it should not be given to patients with renal insufficiency. Rivaroxaban and other DOACs are not used in patients with BMI greater than 40 or weight greater than 120 kg. These agents may also be contraindicated in renal insufficiency, as noted above.

For the morbidly obese patient, optimal doses of UFH, LMWH, and fondaparinux are less certain, but the limited data that are currently available suggest that for patients weighing more than 120 kg, enoxaparin at 1 mg/kg lean body weight every 8 hours is a reasonable choice. An alternative course of action is to use UFH monitored by aPTT or to monitor LMWH dosing with the anti-Xa assay.

Regardless of the form of heparin used, measuring hematocrit and platelet count approximately every 3 days is reasonable to detect asymptomatic anemia or thrombocytopenia. Heparins are typically continued for 5 to 7 days while awaiting 2 to 3 days of targeted warfarin-induced PT (INR) prolongation. DOACs do not require overlap with heparin therapy.

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### Thrombolytic Therapy

Unquestionably, thrombolytic agents accelerate the rate of clot resolution, sometimes dramatically. Recent data regarding the use of thrombolysis for ileofemoral deep vein thrombosis demonstrate an almost doubled vein patency at 6 months and significantly less postthrombotic syndrome. Thrombolytic therapy carries with it a risk of significant complications. Most problematic is the risk of hemorrhage, especially intracranial bleeding. Catheter-directed thrombolytic treatment also improves rate of vein patency and seems to have less bleeding risk than systemic administration of ileofemoral or peripheral thrombolytic therapy. Contraindications include any condition that predisposes to serious bleeding (especially brain or spinal cord conditions) (Table 23-2). Puncture of noncompressible venous sites (e.g., subclavian) should be avoided while thrombolytic agents are administered. By weighing the risk-benefit ratio, it seems reasonable to reserve thrombolytic drugs for patients with proven massive PE (1) with shock or (2) with refractory hypoxemia or (3) for those with limb-threatening leg swelling from DVT. When used, these drugs should be initiated as soon as possible after the thrombotic event has been confirmed. In general, intravenous systemic thrombolytic therapy is administered for acute and life-threatening PE. Although a rationale exists to use catheter-based thrombolytic therapy in the setting of pulmonary emboli, supportive data are limited in comparison to data for treatment of ileofemoral deep vein thrombosis. No comparative trials provide the optimum dosing regimen for thrombolytic agents, but currently, accelerated (1 to 2 hours) administration of tissue plasminogen activator is the most popular approach. Antithrombin therapy is begun as thrombin time
and aPTT fall to approximately 1.5 times normal. Warfarin can be initiated simultaneously with UFH or LMWH. Aminocaproic acid can be used topically to stop local oozing or systemically to counteract thrombolysis if serious bleeding occurs. Reversal of the coagulation disorder also can be accomplished with fresh frozen plasma or cryoprecipitate.

### Table 23-2. Absolute and Relative Contraindications to Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Absolute Contraindications</th>
<th>Relative Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active bleeding other than menses</td>
<td>Systolic BP &gt; 180 mm Hg or diastolic BP &gt; 110 mm Hg</td>
</tr>
<tr>
<td>Malignant intracranial neoplasm (primary or metastatic)</td>
<td>Active bleeding in past 4 wk</td>
</tr>
<tr>
<td>Cardiovascular anomaly (e.g., AV malformation)</td>
<td>Noncompressible vascular punctures</td>
</tr>
<tr>
<td>Suspected aortic dissection</td>
<td>Major surgery in past 3 wk</td>
</tr>
<tr>
<td>Ischemic stroke within 3 mo (but not within 3 h)</td>
<td>Traumatic or prolonged (&gt;10 min) CPR</td>
</tr>
<tr>
<td>Prior history of intracranial hemorrhage</td>
<td>Ischemic stroke over 3 months ago</td>
</tr>
<tr>
<td>Significant closed-head or facial trauma in past 3 mo</td>
<td>Dementia</td>
</tr>
<tr>
<td></td>
<td>Active peptic ulcer disease</td>
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<tr>
<td></td>
<td>Pregnancy</td>
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<td>Ongoing therapy with warfarin</td>
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### Cavaf Interruption and Embolectomy

Percutaneous IVC filter placement, under X-ray or US guidance, can block passage of large clots from the legs and pelvis to the lungs. With some devices, medication may be infused as well through a dedicated part (Fig. 23-6). These devices are generally used when there is a contraindication to anticoagulation therapy. One risk of these devices is development of thrombosis at the filter. Consequently, a standard course of anticoagulation should be administered once contraindications to anticoagulation resolve. If possible, the filter should be removed once therapy is safely accomplished. It is unclear if retrievable filters placed in patients at high risk of death reduce PE-related mortality. Inferior vena cava filter placement in addition to anticoagulation does not improve survival in patients with deep vein thrombosis except in those with hemodynamically unstable PE or after thrombolytic therapy. Insertion of filters increases the risk of recurrent deep vein thrombosis, a fact that offsets some of the benefits attributable to reduced PE. Although deployment of a removable filter is often rational, in practice, many of the removable filters are never extracted. Despite limited data, it is reasonable to perform caval filtration for patients who (1) have proven residual pelvic or lower extremity clot and recurrent life-threatening PE despite adequate anticoagulation, (2) cannot receive thrombolytic therapy or anticoagulation safely, (3) suffer massive embolism or paradoxical emboli, (4) develop septic embolism from the lower extremities, or (5) clearly could not withstand the hemodynamic effects of another embolism. Obviously, IVC filters have no effect on embolic risk if the source is in the upper extremities.
FIGURE 23-6. Vena cava filter with drug infusion port.

Because the procedure must be accomplished rapidly and requires cardiopulmonary bypass, emergent embolectomy is rarely successful. In most successful cases, the patient was already in the operating suite for another reason and was fortunate enough to have a thoracic surgical team and bypass setup available within minutes. Fortunately, most patients surviving long enough for the diagnosis of PE to be made will respond to thrombolytic or anticoagulant therapy. It is only in those patients who are gravely ill and deteriorating despite treatment that surgical therapy or procedures in the interventional radiology suite should be considered. On the other hand, a surgical approach to chronic, persistent central emboli may offer the only chance of relieving disability and potentially lethal pulmonary hypertension. For patients with suspected chronic thrombotic pulmonary hypertension abnormalities can be confirmed by pulmonary angiography. Although less risky than an acute procedure, embolectomy for chronic thrombotic pulmonary artery disease is infrequently employed and candidates must be carefully selected. Catheter-based suction embolectomy may be considered in patients with large proximal acute PE burden in centers where appropriate interventional radiology support is available. There
are limited data available regarding these procedures in a group of patients who present with a significant risk of mortality. Acute management of VTE is summarized in Figure 23-7.

**Long-Term Therapy**

Regardless of the acute treatment chosen, at least 3 months of anticoagulation is indicated. The goal in long-term therapy is to deter clot recurrence by maintaining an INR of 2 to 3. Patients with inherited thrombophilias may require more intense anticoagulation. The INR should be in the therapeutic range for 2 to 3 days before heparin is stopped. Typically a 5-day overlap is necessary because initial prolongations of the PT (because of factor VII depletion) occur well before all components of the vitamin K-dependent pathway are depleted, during which time clotting is still possible. Most of the time a patient spends in the hospital is waiting for warfarin effect, and no credible evidence indicates that patients must receive a fixed period of heparin before warfarin can be safely initiated. Thus, it makes sense to start warfarin simultaneously with heparin. Although controversial, initial warfarin doses of 10 mg are safe and reduce the time to therapeutic effect compared to the commonly used 5-mg dose.

The duration of warfarin anticoagulation must reflect not only the risk for recurrence and its potential physiologic consequences but also the risk of the therapy itself. Because the rate of recurrence falls rapidly with time from embolization, full anticoagulation for ≥3 months has become the standard in most situations.
However, each time the duration of anticoagulation has been studied, it appears that longer periods are associated with a reduced risk of recurrence but only a slightly higher bleeding risk. Patients at continued high risk of recurrence, including those with genetic thrombophilias, anticardiolipin antibodies, and uncured cancer, and patients who have had two or more thrombotic episodes should probably be anticoagulated indefinitely, unless bleeding risk is prohibitive.

Historically, for most patients with deep vein thrombosis or PE, vitamin K antagonist such as warfarin effectively prevents recurrent thrombosis. New oral anticoagulant medications are now available, and the latest iteration of treatment guidelines recommends consideration of dabigatran, rivaroxaban, edoxaban, and apixaban over warfarin therapy in patients without cancer. In a patient with deep vein thrombosis complicating cancer, LMWH is recommended over the new oral anticoagulants and warfarin. Patients with recurrent VTE should be considered for LMWH therapy. With introduction of new therapeutic agents and increasing clinical data, ongoing change in these recommendations is anticipated.

**SUGGESTED READINGS**


Chapter 24
Oxygenation Failure, ARDS, and Acute Lung Injury

Key Points

1. Six mechanisms may contribute to arterial oxygen desaturation: (1) inhalation of a hypoxic gas mixture, (2) alveolar hypoventilation, (3) impaired diffusion of oxygen across the alveolus, (4) $\frac{V}{Q}$ mismatching, (5) shunting of systemic venous blood to the systemic arterial circuit, and (6) abnormal desaturation of systemic venous blood in the presence of a $\frac{V}{Q}$ abnormality or shunt.

2. Clues to the nature of an oxygenation crisis are offered by radiographic appearance. Lung collapse (atelectasis), diffuse or patchy parenchymal infiltration, fluid overload, localized or unilateral infiltration, and a clear chest radiograph are distinct patterns that suggest specific etiologies and approaches to treatment. Chest CT provides invaluable information to resolve overlapping shadows of lung parenchyma, pleural space, and chest wall.

3. Atelectasis is perhaps the most common cause of hypoxemia for the bedridden, critically ill, and postoperative patient. Potential consequences are worsened gas exchange, pneumonitis, and increased work of breathing. Mobilization, continuous positive airway pressure, and assiduous bronchial hygiene are keys to successful prevention and management.

4. Acute respiratory distress syndrome is characterized by a delay between a characteristic precipitating event and the onset of dyspnea, impaired respiratory system compliance that results primarily from the loss of functional lung units, markedly reduced aerated lung volume, hypoxemia refractory to modest concentrations of inspired oxygen, diffuse pulmonary infiltrates, and absence of a purely hemodynamic cause. Associated high-protein alveolar edema resolves more slowly than hydrostatic edema and is more likely to generate a patchy distribution and detectable air bronchograms.

5. Basic therapeutic principles in treating an oxygenation crisis are to minimize the risk:benefit ratio of ventilation by accepting hypercapnia in preference to high tidal volumes and ventilating pressures, to adequately recruit the lung, and to minimize tissue oxygen demand and ventilation requirements (e.g., by sedation).

6. Shifts of body position alter the regional distributions of ventilation and volume. Prone positioning clearly alters the regional distribution of transpulmonary pressure and may dramatically improve arterial oxygenation.

7. Manipulation of peak, mean, and end-expiratory alveolar pressures plays a crucial role in achieving adequate arterial oxygenation at an acceptable $FIO_2$. Recruiting maneuvers increase the transpulmonary pressure enough to open refractory lung units, especially those in gravitationally dependent zones. End-expiratory alveolar pressure (total positive end-expiratory pressure, the sum of positive end-expiratory pressure and auto-positive end-expiratory pressure) helps maintain patency of alveolar units at risk for collapse. During passive inflation, mean airway pressure reflects average lung size and correlates with oxygenation efficiency.

8. High tidal volume/low positive end-expiratory pressure strategies may extend alveolar injury or retard healing of already-injured tissues. Avoiding excessive transpulmonary stretching (plateau and driving) pressures during tidal inflation while maintaining sufficient end-expiratory transpulmonary pressure is a rational ventilatory strategy. This “lung-protective” approach often results in low tidal volumes (depending
on lung compliance) and the need to accept CO\(_2\) retention (permissive hypercapnia).

9. Many choices for ventilatory mode are equally defensible, as long as the practitioner ensures adequate oxygen delivery, follows similar guidelines for lung protection, and remains alert to the potential shortcomings and complications of the mode in use.

10. The essential elements of a lung-protective approach to ventilating acute respiratory distress syndrome are (1) to minimize oxygen and ventilation demands, using neuromuscular blockade when necessary, (2) to apply sufficient end-expiratory pressures to establish and maintain recruitment of most unstable but functional alveoli, (3) to avoid overstretching the lung, (4) to accept moderate hypercapnia unless there is a serious neurologic or cardiovascular contraindication, (5) to implement prone positioning in the difficult-to-oxygenate patient, and (6) to avoid fluid excess and sustained application of high concentrations of inspired oxygen. (7) Extracorporeal gas exchange may be needed in unusually difficult cases as a rescue measure when violation of these principles cannot otherwise be avoided.

**OXYGENATION FAILURE: DEFINITION**

Respiratory failure may be considered a problem in one or more of the steps necessary to sustain mitochondrial energy production. Dysfunction may occur in ventilation (the movement of gases between the environment and the lungs; see Chapter 25), in intrapulmonary gas exchange (the process in which mixed venous blood releases CO\(_2\) and becomes oxygenated), in gas transport (the delivery of adequate quantities of oxygenated blood to the metabolizing tissue), or in tissue gas exchange (the extraction or use of O\(_2\) and release of CO\(_2\) by the peripheral tissues).

The latter two steps in this process may fail independently of the performance of the lung or ventilatory pump, as in severe sepsis. Tissue O\(_2\) delivery depends not only on the partial pressure of arterial oxygen (PaO\(_2\)) but also on the nonpulmonary factors—cardiac output, hemoglobin (Hgb) concentration, distributional efficiency, and the ability of Hgb to take up and release O\(_2\). Cardiogenic shock, severe anemia, and carbon monoxide poisoning provide clinical examples of O\(_2\) transport failure (see Chapter 38).

Laboratory abnormalities characteristic of such conditions are lactic acidosis and reduced O\(_2\) content of mixed venous blood (even in the face of adequate arterial oxygen tension).

Failure of O\(_2\) uptake refers to the inability of the tissue to extract and use O\(_2\) for aerobic metabolism. The clearest clinical examples of a derangement in this terminal phase of the oxygen transport chain are septic shock and cyanide poisoning, in which cellular cytochromes (key enzymes in the electron transport process) are inhibited. During sepsis, there is failure of an often generous cardiac output to distribute appropriately and/or an inability of the mitochondria themselves to make use of the O\(_2\) available. Unlike transport insufficiency, failure of tissue uptake implies insufficient O\(_2\) extraction and, therefore, may be associated with normal or even high values for mixed venous oxygen tension, saturation, and content. Some indices that are helpful in other forms of oxygenation failure (i.e., cardiac output, arterial O\(_2\) tension, and central or mixed venous O\(_2\) saturations [S\([v \text{ with bar above}]O_2\)]) may not reflect impaired tissue O\(_2\) uptake reliably; lactic acid levels and trends, though imprecise, may be the most useful blood indicators. Therapy directed at failure of the O\(_2\) transport mechanism is discussed in detail elsewhere (see Chapters 1 and 3). The following discussion focuses on the problems that bear on the gas exchanging performance of the lung.
MECHANISMS OF ARTERIAL HYPOXEMIA

Six mechanisms may contribute to arterial oxygen desaturation (Table 24-1):

1. Inhalation of a hypoxic gas mixture or ascent to altitude
2. Hypoventilation
3. Impaired alveolar diffusion of oxygen
4. Ventilation-perfusion ([V with dot above]/{Q with dot above}) mismatching
5. Shunting of systemic venous blood to the systemic arterial circuit
6. Abnormal desaturation of systemic venous blood in conjunction with cause 3, 4, or 5

Low Inspired Oxygen Fraction

A decrease in the partial pressure of inhaled oxygen occurs in toxic fume inhalation, in closed-space fires that consume O₂ in combustion, and at high altitudes because of reduced barometric pressure. In this “low fraction of inspired oxygen (FiO₂)” context, it should not be forgotten that very rarely, unsuspected disconnection from supplemental oxygen precipitates hypoxemia.

Table 24-1. Mechanisms of Arterial Hypoxemia

<table>
<thead>
<tr>
<th>Low inspired FiO₂</th>
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<tbody>
<tr>
<td>Hypoventilation</td>
</tr>
<tr>
<td>Impaired diffusion</td>
</tr>
<tr>
<td>([V with dot above]/[Q with dot above]) mismatching</td>
</tr>
<tr>
<td>Shunt</td>
</tr>
<tr>
<td>Desaturated mixed venous blood°</td>
</tr>
</tbody>
</table>

°In the presence of other mechanisms for hypoxemia.

Hypoventilation

Hypoventilation causes the partial pressure of alveolar oxygen (PAO₂) to fall when alveolar oxygen is not replenished quickly enough in the face of its ongoing removal by the blood. Although PaO₂ may fall much faster than PaCO₂ rises during the initial phase of hypoventilation or apnea, the steady-state concentration of PaO₂ is predicted by the simplified alveolar gas equation:
In this equation, $P_{iO_2}$ is the partial pressure of the inspired oxygen at the tracheal level (corrected for water vapor pressure at body temperature), and $R$ is the respiratory exchange ratio (i.e., the ratio of $CO_2$ production to oxygen consumption at steady state). Transiently, $R$ can fall to very low values because oxygen is taken up faster than $CO_2$ is delivered to the alveolus. Such a mechanism explains posthyperventilation hypoxemia and may contribute to hypoxemia that accompanies hemodialysis.

**Impaired Diffusion**

Impaired diffusion of oxygen prevents complete equilibration of alveolar gas with pulmonary capillary blood. Although this mechanism has uncertain clinical importance, many factors that adversely influence diffusion are encountered in the critically ill, for example, increased distance between alveolus and erythrocyte and shortened transit time of the red cell through the capillary (high cardiac output with limited capillary reserve).

**Ventilation-Perfusion Mismatching**

$[V \; \text{with dot above}]/[Q \; \text{with dot above}]$ mismatching is the most frequent contributor to clinically important $O_2$ desaturation. Lung units that are poorly ventilated in relation to perfusion cause desaturation; high $[V \; \text{with dot above}]/[Q \; \text{with dot above}]$ units contribute to physiologic dead space but not to hypoxemia. The relationship of $O_2$ content to $PaO_2$ is curvilinear. At normal barometric pressure, little additional $O_2$ can be loaded onto the blood with already saturated Hgb, no matter how high the $O_2$ tension in the overventilated alveolus may rise. Because samples of blood exiting from different lung units mix gas contents (not partial pressures), overventilating some units in an attempt to compensate for others that are underventilated does not maintain $PaO_2$ at a normal level. Therefore, when equal volumes of blood from well-ventilated and poorly ventilated units mix, the blended sample will have $O_2$ content halfway between them but $PaO_2$ disproportionately weighted toward that of the lower $[V \; \text{with dot above}]/[Q \; \text{with dot above}]$ unit. Even though minute ventilation ($V_E$) and cardiac output ($[Q \; \text{with dot above}]$) may be absolutely normal, regional $[V \; \text{with dot above}]/[Q \; \text{with dot above}]$ mismatching will cause $PaO_2$ to fall.

A high concentration of inspired $O_2$ will correct hypoxemia when $[V \; \text{with dot above}]/[Q \; \text{with dot above}]$ mismatching, hypoventilation, or diffusion impairment is the cause. (The $PaO_2$ of even poorly ventilated units climbs high enough to achieve full saturation.) After breathing 100% $O_2$ for a sufficient period of time, only perfused units that are totally unventilated (shunt units) contribute to hypoxemia. However, when hypoxemia is caused by alveolar units with very low $[V \; \text{with dot above}]/[Q \; \text{with dot above}]$ ratios, relatively concentrated $O_2$ mixtures must be given before a substantial change in the $PaO_2$ is observed (see Fig. 5-2 in Chapter 5).

**Shunting**

The term *shunt* refers to the percentage of the total systemic venous blood flow that bypasses the gas exchanging membrane and transfers venous blood unaltered to the systemic arterial system. Changes in $FiO_2$—either upward or downward—have very little influence on $PaO_2$ when the true shunt fraction, as measured on pure oxygen, exceeds 30% (Fig. 24-1). In contrast, venous admixture of similar magnitude is variably responsive, to the extent that low $[V \; \text{with dot above}]/[Q \; \text{with dot above}]$ units account for the hypoxemia. Shunt can be cardiovascular, as in cyanotic right-to-left congenital heart disease, the opening of a patent foramen ovale because of elevated right ventricular pressures, or the passage of blood through abnormal vascular channels within the lung (pulmonary arteriovenous malformations). However, by far, the most common cause of shunting is
pulmonary disease characterized by unventilated alveolar spaces that cannot respond to oxygen therapy. After an extended exposure to an FiO\textsubscript{2} of 1.0, all alveoli that remain open are filled with pure oxygen. (Some absorption atelectasis may occur in very low [V \text{ with dot above}] [Q with dot above] areas when pure oxygen is breathed, adding to the measured shunt. In the clinical setting, however, the magnitude of this artifact usually is small.) The fraction of blood shunted across the lung from all sources (Q\textsubscript{s}/Q\textsubscript{T}) can be calculated by the following formula:

\[
\frac{Q_s}{Q_T} = \frac{[(CcO_2 - CaO_2)/(CcO_2 - CvO_2)]}{((CcO_2 - CaO_2)/(CcO_2 - CvO_2))}
\]

In this equation, C denotes content, and the lower case letters c, a, and v denote end-capillary, arterial, and mixed venous blood, respectively. In making such calculations, end-capillary and calculated alveolar oxygen tensions are assumed equivalent. For a patient breathing pure O\textsubscript{2}, shunt percentages lower than 25% can be estimated rapidly by dividing the alveolar to arterial O\textsubscript{2} tension difference (approx. 670—PaO\textsubscript{2}) by 20, assuming also that the PaCO\textsubscript{2} and CvO\textsubscript{2} are normal. For example, if measured PaO\textsubscript{2} is 270 mm Hg, estimated shunt is 400/20, or 20%.

FIGURE 24-1. Relationship of arterial oxygen tension (PaO\textsubscript{2}) to true shunt fraction ([Q with dot above]_s/[Q with dot above]_T) for three values of inspired oxygen fraction (FiO\textsubscript{2}). Variations of FiO\textsubscript{2} exert negligible effects on PaO\textsubscript{2} when true shunt exceeds 30%.
At inspired oxygen fractions lower than 1.0, true shunt cannot be estimated reliably by an analysis of oxygen contents, but “venous admixture” or “physiologic shunt” can. (Some publications erroneously refer to venous admixture from all causes as “shunt.”) Any degree of arterial O\textsubscript{2} desaturation can be considered as if it all originated from true shunt units. To calculate venous admixture, C\textsubscript{cO\textsubscript{2}} in the shunt formula is estimated from the ideal alveolar PO\textsubscript{2} at that particular fraction of inspired oxygen (FiO\textsubscript{2}).

Many indices have been devised in an attempt to characterize the efficacy of oxygen exchange across the full spectrum of FiO\textsubscript{2} values. Although no index is completely successful, the PaO\textsubscript{2}:PAO\textsubscript{2} ratio and the alveolar to arterial oxygen tension difference (A − a)O\textsubscript{2} are often used (see Chapter 5). Both, however, are affected by changes in S\{v with bar above\}O\textsubscript{2}, even when the lung tissue itself is unaltered from its diseased baseline. Another imprecise but perhaps most commonly used indicator of oxygen exchange is the PaO\textsubscript{2}:FiO\textsubscript{2} ratio (the P:F ratio). Changing PEEP and mean airway pressure alters this index. In healthy adults, PaO\textsubscript{2}:FiO\textsubscript{2} normally exceeds 400, whatever the FiO\textsubscript{2} may be. In the absence of FiO\textsubscript{2}-related absorption atelectasis or cardiovascular adjustments, hypoventilation and changes in the inspired O\textsubscript{2} concentration minimally alter the ratios just discussed.

**Abnormal Desaturation of Systemic Venous Blood**

The admixture of abnormally desaturated venous blood is an important mechanism acting to lower the PaO\textsubscript{2} in patients with impaired pulmonary gas exchange and reduced cardiac output. CvO\textsubscript{2}, the product of Hgb concentration and S\{v with bar above\}O\textsubscript{2}, is influenced by cardiac output (Q), arterial oxygen saturation (SaO\textsubscript{2}), and oxygen consumption (VO\textsubscript{2}):

\[
S\{v with bar above\}O_2 \approx SaO_2 - \left[ VO_2 / (Hgb \times Q) \right]
\]

It is clear from this equation that S\{v with bar above\}O\textsubscript{2} is directly influenced by any imbalance between VO\textsubscript{2} and oxygen delivery. Thus, anemia that is inadequately compensated by an increase in cardiac output or a cardiac output too low for metabolic needs in a nonanemic patient can cause both S\{v with bar above\}O\textsubscript{2} and PaO\textsubscript{2} to fall when the venous admixture percentage is abnormal.

Fluctuations in S\{v with bar above\}O\textsubscript{2} exert a more profound influence on PaO\textsubscript{2} when the shunt is fixed, as in regional lung diseases (e.g., atelectasis), than when the shunt varies with changing cardiac output, as it tends to do in diffuse lung injury (acute respiratory distress syndrome [ARDS]) (Fig. 24-2). Even when S\{v with bar above\}O\textsubscript{2} is abnormally low, PaO\textsubscript{2} will remain unaffected if all mixed venous blood gains access to well-oxygenated, well-ventilated alveoli. (A marked decline in S\{v with bar above\}O\textsubscript{2} without arterial hypoxemia routinely occurs during heavy exercise in healthy subjects.)

Therefore, abnormal [\textit{V with dot above}] / [\textit{Q with dot above}] matching or shunt is necessary for venous desaturation to contribute to hypoxemia.
Variations in $S\bar{v}O_2$ related to an oxygen consumption/delivery imbalance have minimal effects on $PaO_2$ in normal subjects but may profoundly affect $PaO_2$ in patients with extensive lung disease.

**DISEASE-INDUCED HYPOXEMIA**

Oxygenation disorders can be categorized by their radiographic appearances, which give important clues to the appropriate management approach. Lung collapse (atelectasis), diffuse or patchy parenchymal infiltration, hydrostatic edema, localized or unilateral infiltration, and a clear chest radiograph are common patterns (Fig. 24-3).
FIGURE 24-3. Radiographic patterns associated with hypoxemia.

Atelectasis

Variants of Atelectasis

There are several morphologic types and mechanisms of atelectasis. Regional microatelectasis develops spontaneously in a healthy lung during shallow breathing when it is not periodically stretched beyond its usual tidal range. Platelike atelectasis may be an exaggeration of this phenomenon because of regional hypodistension (e.g., secondary to pleural effusion or impaired diaphragmatic excursion). Both microatelectasis and platelike atelectasis occur most commonly in dependent regions, especially in obesity. Lobar collapse usually results from gas absorption behind an airway plugged by retained secretions, a misplaced endotracheal tube, bronchial compression by the heart or pleural effusion, or a large airway mass. Microatelectasis and platelike atelectasis occur routinely in patients on prolonged, uninterrupted bed rest and in postoperative patients who have undergone upper abdominal incisions.

Potential consequences of acute atelectasis are worsened gas exchange, pneumonitis, and increased work of breathing. PaO$_2$ drops precipitously to its nadir within minutes to hours of sudden bronchial occlusion, but it then improves steadily over hours to days as hypoxic vasoconstriction and mechanical factors increase pulmonary vascular resistance through the affected area. Whether an individual patient manifests hypoxemia depends heavily on the vigor of the hypoxic vasoconstrictive response, the abruptness of collapse, and the tissue volume involved. If small areas of atelectasis develop slowly, hypoxemia may never surface as a clinical problem.

Diffuse microatelectasis may be radiographically silent but detectable on physical examination by dependent (posterior or basilar) end-inspiratory rales, which improve after several sustained deep breaths (sighs) or coughs. Platelike atelectasis yields similar physical findings plus tubular breath sounds and egophony over the involved area. Lobar atelectasis gives a dull percussion note and diminished breath sounds if the bronchus is occluded by secretions, but bronchial breath sounds and egophony are heard if the central airway is patent. (The latter findings correlate well with the presence of air bronchograms on chest radiograph.) Platelike atelectasis develops most frequently at the lung base above a pleural effusion or above a raised, splinted, or
immobile hemidiaphragm. Obesity predisposes to all forms of atelectasis. Lobar atelectasis occurs commonly in patients with copious airway secretions and limited power to expel them. Acute upper lobe collapse occurs less commonly and tends to resolve quickly because of comparatively good gravitational drainage and greater local transpulmonary pressure. Collapse of the left lower lobe is more frequent than collapse of the right lower lobe, perhaps because of its retrocardiac position and its smaller caliber, sharply angulated bronchus. Lobar atelectasis may be complete or partial, but in either case, it is radiographically recognized by opacification in an anatomically geographic distribution, displaced fissures and hilum, compensatory hyperinflation of surrounding tissue, narrowed rib interspaces, and obliterated air/soft tissue boundaries (see Chapter 11). Small amounts of pleural fluid form as an expected consequence of lobar collapse and do not necessarily signify an additional pathologic process.

Management of Atelectasis

Prophylaxis

Effective prevention of atelectasis in high-risk patients counteracts shallow breathing, maintains adequate transpulmonary pressure by appropriate positioning or airway pressure, and avoids secretion retention. Obesity, chronic bronchitis, impaired airway clearance, neuromuscular weakness, regional chest wall trauma, recent thoracic or abdominal surgery, and advanced age are predisposing factors. Atelectasis is to be expected whenever the patient is prevented from taking a deep breath by pain, splinting, or weakness. Upper abdominal, lateral chest, midline chest, and lower abdominal incisions are associated with the highest incidence of postoperative atelectasis (in that order). Preoperatively, the airways should be maximally dilated and free of infection. Postoperatively, patients should be encouraged to breathe deeply, to sit upright, and to cough vigorously. Pain should be relieved but alertness preserved. Drainage of excess pleural fluid or ascites deserves consideration. Frequent turning and early mobilization are among the most important prophylactic measures. Continuous positive airway pressure (CPAP) may be helpful, especially for intubated patients. Respiratory therapy (RT) techniques such as airway suctioning, incentive spirometry, and chest vibropercussion (if tolerated) are prophylactically as well as therapeutically effective in well-selected patients (see Chapter 18).

Treatment

Whenever possible, mobilization is a highly effective treatment. Periodic deep breathing effectively reverses platelike atelectasis and microatelectasis. Sustained deep breathing is particularly useful. Whether a higher lung volume is achieved by positive airway pressure or by negative pleural pressure is immaterial, assuming that a similar extent and distribution of distension occurs in both cases. Adequate PEEP or CPAP is accepted as routine in the treatment of established collapse. Relief of severe chest wall pain helps reduce splinting and enables more effective coughing. Intercostal nerve blocks with anesthetic agents such as bupivacaine may be effective for 8 to 12 hours. Epidural narcotics also may be effective in certain settings. Retained secretions must be dislodged from the central airways. For the unintubated patient, effective bronchial hygiene is inconsistently accomplished with blind tracheal suctioning alone. Nasopharyngeal airways certainly help, but they are not well tolerated by patients who are awake and are not intended for extended care (see Chapter 6). Vigorous RT initiated soon after the onset of lobar collapse (which may include postural maneuvers and/or vibropercussion) can reverse most atelectasis because of airway plugging within 24 to 48 hours. As a rule, fiberoptic bronchoscopy should be reserved for patients with symptomatic lobar collapse who lack central “air bronchograms” that branch into the collapsed zone and who cannot undergo (or fail to respond to or tolerate) 48 hours of vigorous RT. Even whole lung collapse usually merits at least one RT treatment (including stimulated cough and tracheal suctioning) before bronchoscopy is performed. After reexpansion, a prophylactic positioning
and RT program should be initiated to prevent recurrence. Adjunctive measures (e.g., bronchodilators, hydration, frequent turning, and, in some cases, mucolytics and mucus lubricants) should not be ignored.

**Diffuse Pulmonary Infiltration**

Fluid confined to the interstitial spaces may cause hypoxemia as a result of peribronchial edema, \( [V \text{ with dot above}]/[Q \text{ with dot above}] \) mismatching, and microatelectasis; however, very few processes are confined exclusively to the air spaces or to the interstitium. Radiographic signs of extensive alveolar filling include segmental distribution, coalescence, fluffy margins, air bronchograms, rosette patterns, and silhouetting of normal structures. A diffuse infiltrate is said to be largely “interstitial” if these signs are largely absent and the infiltrate parallels the vascular distribution. Computed tomography imaging greatly increases the diagnostic precision, especially when a thickened or diseased chest wall obscures radiographic features of the lung parenchyma. Any diffuse interstitial process will appear more radiodense at the bases than at the apices, in part because there is more tissue to penetrate and because vascular engorgement tends to be greater there. Gravitationally dependent alveoli also are less distended, so the ratio of aerated volume to total tissue volume declines.

**FIGURE 24-4.** Radiographic patterns in patients with impaired oxygenation because of congestive heart failure (A), vascular congestion because of volume overload (B), and ARDS (C). Kerley lines, widened vascular pedicle, costophrenic angle sparing, blurred hilar structures, and paucity of air bronchograms help distinguish congestive heart failure from ARDS. (Modified from Milne EN, et al. The radiologic distinction of cardiogenic and noncardiogenic edema. *AJR Am J Roentgenol.* 1985;144:879-894, with permission.)

The major categories of acute disease that produce diffuse pulmonary infiltration and hypoxemia are pneumonitis (infection and aspiration), cardiogenic pulmonary edema, intravascular volume overload, and permeability edema (ARDS). From a radiographic viewpoint, these processes may be difficult to distinguish; however, a few characteristic features are helpful.

**Hydrostatic Edema**

Perihilar infiltrates (sparing the costophrenic angles), a prominent vascular pattern, and a widened upper mediastinal vascular width (the pedicle) suggest volume overload or incipient cardiogenic edema (*Fig. 24-4*). A gravitational distribution of edema is highly consistent with well-established left ventricular failure (or long-standing, severe volume overload), especially when accompanied by cardiomegaly and a widened vascular pedicle. Patchy peripheral infiltrates that lack a gravitational predilection and show reluctance to change with position suggest ARDS (*Fig. 24-5*). During the initial phase, a dorsal predominance of infiltrates is often observed...
the axial CT scan (Fig. 24-6). Interestingly, septal (Kerley) lines and distinct peribronchial cuffing are very seldom seen in ARDS without coexisting volume overload (see following). On the other hand, prominent air bronchograms are quite unusual with purely hydrostatic etiologies but occur commonly in permeability edema (ARDS) and pneumonia. It should be recalled that permeable vessels leak fluid even at normal vascular pressures, so mixed patterns of ARDS and hydrostatic edema are often seen.

**FIGURE 24-5.** Left: CT scan image of the lungs in initial stage of ARDS. Right: ARDS in later recovery stage.

**Variants of Hydrostatic Edema**

Hydrostatic pulmonary edema (HPE) may occur in multiple settings that have differing implications for prognosis and treatment. The most familiar form of HPE accompanies left ventricular failure. In this setting, signs of systemic hypoperfusion and inadequate cardiac output often accompany oxygenation failure. However, HPE commonly develops even with a normally well-compensated ventricle during transient cardiac dysfunction (ischemia, hypertensive crisis, arrhythmias, etc.). When the myocardium fails to fully relax during diastole (diastolic dysfunction), volume loading or temporary disturbances of left heart contractility (e.g., ischemia), mitral valve functioning, or heart rate or rhythm may cause rapid, transient alveolar flooding known as “flash pulmonary edema.” In this setting, an impressive radiographic appearance may both develop and resolve quickly.
Acute Lung Injury and ARDS

Definitions and Categories

Prior to the 2012 revision of the American-European Consensus Committee (AECC) definition (Fig. 24-7), acute lung injury (ALI) was a general term applied to all degrees of acutely developing, radiographically apparent, diffuse hypoxemic lung injury of diverse noncardiac etiologies. Acute respiratory distress syndrome (ARDS) was defined as the most severe form of ALI—regardless of age. The unspoken implication of the ARDS label, however, is that the root cause of the infiltrates is high permeability edema secondary to inflammation. Currently, “acute respiratory distress syndrome” (ARDS) is an imprecise and all encompassing term applied to any acute multilobar or diffuse parenchymal infiltration associated with severe hypoxemia on at least 5 cm H$_2$O PEEP and not attributable to HPE. Official definitions for use in clinical trials (e.g., published by the Berlin consensus) are quite liberal and do not specify the exact characteristics of the acute infiltrates, nor the mechanical properties of the thorax, nor the exact conditions under which the oxygenation data are gathered (e.g., position). Up to 7 days may elapse before clinical presentation. Experts frequently disagree on whether a radiograph is consistent with “ARDS,” and modifications of PEEP and/or position often can move a potential candidate into or out of an ARDS category. Given these definitional shortcomings, it may not be surprising that relatively few “positive” therapeutic trials in ALI/ARDS have appeared, even though the mortality of patients with similar severity of physiologic impairment has clearly declined over the past decades. The ARDS designation may be most useful...
when restricted to acute noncardiogenic pulmonary edema that is diffusely distributed and patchy and has certain characteristic features:

### Berlin Definition of ARDS 2012

<table>
<thead>
<tr>
<th>柏林定义 2012年 ARDS</th>
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<tbody>
<tr>
<td><strong>急性呼吸窘迫综合症</strong> (Acute Respiratory Distress Syndrome)</td>
</tr>
<tr>
<td><strong>时机</strong> (Timing)</td>
</tr>
<tr>
<td><strong>胸影像</strong> (Chest Imaging)</td>
</tr>
<tr>
<td><strong>起源的水肿</strong> (Origin of Edema)</td>
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<tr>
<td><strong>血氧学</strong> (Oxygenation)</td>
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**图24-7. “柏林”修订的ARDS合并症定义的临床试验摘要。** 注意无呼吸力学指标。

1. 短暂延迟至事件发生和迅速出现呼吸困难
2. 呼吸系统转导障碍
3. 显著减少肺内血流量
4. 静脉压对低水平的吸入性氧和PEEP无反应
5. 延迟恢复

**主要（肺部） vs. 二次（非肺部）急性肺损伤**

急性肺损伤的病理生理学几乎是肯定地取决于引起事件的类型。尽管其原因很多，但感染、肺炎、吸入性损伤和多发性损伤在大多数病例中占主导地位。到时那些ARDS临床诊断的患者，尸检的病理学变化往往与典型描述的有所不同。

一种有用的方法是将“主要”ARDS分类，即将损伤发生在肺泡或肺泡水平（如，肺炎），与初始血管内皮损伤事件（“二次”或“非肺部”ARDS）有所不同。一些数据支持这一论点，即主要患者比二次患者更少使用机械通气。尽管存在这些差异，ARDS的核心病理生理学是相似的，因此需要采取一致的治疗策略。

所有形式ARDS的一个明显特征是损伤到肺泡-毛细血管膜，无论是气体侧（如，吸入性损伤、吸入性酸）还是血液侧（如，感染、脂肪栓塞）。膜透性增加导致蛋白性液体渗入间质和肺泡空间。这些液体抑制表面活性剂，导致广泛性肺泡塌陷，减少通气能力（所谓的ARDS婴儿肺），以及需要增加压力来保持肺泡的开放和功能。开放的肺泡具有相对正常的机械顺应性。在严重疾病的发展过程中，肺血管阻力和一定程度的肺高压常常不可逆转。极度肺高压预后不良。偶尔，肺高压的发展导致右心室压力升高，从而导致右向左的分流，通过心脏。通过商业性对比剂或剧烈液体（气泡试验）的超声心动图可以检测到这种情况。

**主要（肺部） vs. 二次（非肺部）急性肺损伤**

急性肺损伤的病理生理学几乎是肯定地取决于引起事件的类型。尽管其原因很多，但感染、肺炎、吸入性损伤和多发性损伤在大多数病例中占主导地位。到时那些ARDS临床诊断的患者，尸检的病理学变化往往与典型描述的有所不同。

一种有用的方法是将“主要”ARDS分类，即将损伤发生在肺泡或肺泡水平（如，肺炎），与初始血管内皮损伤事件（“二次”或“非肺部”ARDS）有所不同。一些数据支持这一论点，即主要患者比二次患者更少使用机械通气。尽管存在这些差异，ARDS的核心病理生理学是相似的，因此需要采取一致的治疗策略。

所有形式ARDS的一个明显特征是损伤到肺泡-毛细血管膜，无论是气体侧（如，吸入性损伤、吸入性酸）还是血液侧（如，感染、脂肪栓塞）。膜透性增加导致蛋白性液体渗入间质和肺泡空间。这些液体抑制表面活性剂，导致广泛性肺泡塌陷，减少通气能力（所谓的ARDS婴儿肺），以及需要增加压力来保持肺泡的开放和功能。开放的肺泡具有相对正常的机械顺应性。在严重疾病的发展过程中，肺血管阻力和一定程度的肺高压常常不可逆转。极端肺高压预后不良。偶尔，肺高压的发展导致右心室压力升高，从而导致右向左的分流，通过心脏。通过商业性对比剂或剧烈液体（气泡试验）的超声心动图可以检测到这种情况。
a worthwhile undertaking in cases of hypoxemia refractory to usual measures. Diffuse pulmonary infiltration with a normal wedge pressure can be seen in other problems, such as flash pulmonary edema and partially treated heart failure. Apart from any difference in capillary pressure, permeability edema differs from hydrostatic edema in that it resists clearance by diuretic therapy and initiates a cellular inflammatory response that may require weeks to recede and even longer to heal.

**Rapidly Resolving Noncardiogenic Edema**

A few disorders that fall loosely under the heading of ARDS are worth noting because of their fundamentally different pathophysiology and clinical course. In certain settings, transient disruption in the barrier function of the pulmonary capillary can occur without severe endothelial damage. Neurogenic and heroin-induced pulmonary edema, for example, are two problems in which a transiently elevated pulmonary venous pressure is believed to open epithelial tight junctions, forcing extravasation of fluid. However, barrier resealing and resolution of edema occur promptly without widespread endothelial damage or protracted inflammation. A similar process may be seen in settings such as severe metabolic acidosis and cardiopulmonary resuscitation. From the alveolar side, certain inhalational injuries (e.g., limited chlorine or ammonia gas exposure) can produce a dramatic initial picture, only to clear rapidly over a brief period. Pulmonary edema that follows reexpansion of lung compressed by air or fluid may relate partially to the negative pressures developed during the procedure and to the deficiency of functional surfactant that characterizes airless lung.

**Hypoxemia with a Clear Chest Radiograph**

Uncommonly, patients present with new-onset, lifethreatening hypoxemia without major radiographic “plain film” evidence of infiltration. In such cases, occult shunting and severe \[V \text{ with dot above}] / \[Q \text{ with dot above}\] mismatching are the most likely mechanisms (Table 24-1). Despite an unremarkable plain chest film, computed tomography almost invariably shows evidence for “ground glass” infiltration that signifies microcollapse and/or lung edema. Intracardiac or intrapulmonary shunts, asthma and other forms of airway obstruction, low lung volume superimposed on a high closing capacity (e.g., bronchitis in a supine obese patient), pulmonary embolism, and occult microvascular communications (such as those occurring in patients with cirrhosis) are potential explanations. Hypoxemia of most causes is amplified by profound desaturation of mixed venous blood, by reversal of hypoxic vasoconstriction with therapeutic vasoactive agents (e.g., nitroprusside, calcium channel blockers, and dopamine), and by the severe \[V \text{ with dot above}] / \[Q \text{ with dot above}\] imbalance occasionally encountered after acute head injury.

**Unilateral Lung Disease**

Unilateral infiltration or marked asymmetry of radiographic density suggests a confined set of etiologic possibilities, most of which occur in highly characteristic clinical settings (Fig. 24-3). Marked asymmetry of radiographic involvement should prompt an especially careful search for an unaddressed and readily reversible cause of hypoxemia. In some cases, especially pneumonitis or airway plugging, precautions also should be taken against generalization of the process—“propagation prevention” (see Chapter 8).

**TECHNIQUES TO IMPROVE TISSUE OXYGENATION (TABLE 24-2)**

**Basic Therapeutic Principles**

Although atelectasis, fluid overload, and infection often yield to specific measures, the treatment of diffuse lung injury remains largely supportive. The primary therapeutic aims are to maintain oxygen delivery, to relieve an excessive breathing workload, and to establish electrolyte balance while preventing further damage from oxygen toxicity, barotrauma, ventilator-induced lung injury (VILI), infection, and other iatrogenic complications. To these ends, the clinician should keep a few fundamental principles in mind.
Minimize the Risk/Benefit Ratio

Positive airway pressure, oxygen, and vasoactive drugs are potentially injurious. Therefore, frequent reassessment is indicated of the need for current medications, as well as levels of PEEP and FiO$_2$, and the use and intensity of ventilator support, as indicated by tidal driving pressure and minute ventilation. In well-selected cases, targeting an oxygen saturation greater than 85% may be acceptable if the patient has adequate oxygen-carrying capacity and circulatory reserve without signs of oxygen privation (e.g., lactic acidosis). Similarly, allowing PaCO$_2$ to climb modestly may minimize the ventilatory requirement and reduce the risk of barotrauma (see Permissive Hypercapnia, following, and Chapter 8). Mean intrathoracic pressure can be reduced by allowing the patient to provide as much ventilatory power as possible, compatible with ventilatory capability and comfort.

<table>
<thead>
<tr>
<th>Table 24-2. Techniques to Improve Tissue Oxygenation</th>
</tr>
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<tbody>
<tr>
<td>Increase FiO$_2$</td>
</tr>
<tr>
<td>Increase mean lung volume and mean alveolar pressure</td>
</tr>
<tr>
<td>PEEP/auto-PEEP</td>
</tr>
<tr>
<td>Extend inspiratory time fraction</td>
</tr>
<tr>
<td>Airway pressure release ventilation (APRV)</td>
</tr>
<tr>
<td>Upright or prone positioning</td>
</tr>
<tr>
<td>Bronchodilation</td>
</tr>
<tr>
<td>Improve O$_2$ delivery/consumption ratio</td>
</tr>
<tr>
<td>Reduce O$_2$ requirements</td>
</tr>
<tr>
<td>Minimize work of breathing</td>
</tr>
<tr>
<td>Fever reduction</td>
</tr>
<tr>
<td>Reduce agitation</td>
</tr>
<tr>
<td>Consider neuromuscular relaxants</td>
</tr>
<tr>
<td>Relieve pain</td>
</tr>
<tr>
<td>Treat acidosis</td>
</tr>
<tr>
<td>Extracorporeal membrane oxygenation (ECMO)</td>
</tr>
<tr>
<td>Increase cardiac output</td>
</tr>
<tr>
<td>Correct severe anemia</td>
</tr>
<tr>
<td>Remove systemic pulmonary vasodilators (e.g., nitroprusside)</td>
</tr>
</tbody>
</table>
Consider adjunctive support

Inhaled nitric oxide or inhaled prostacyclin
Extracorporeal membrane oxygenation (ECMO)

Prevent Therapeutic Misadventures

Patients should be kept under direct observation at all times by well-trained personnel. Paralyzed patients must be watched with special care, because ventilation is totally machine dependent. Furthermore, the hands must be restrained in semiconscious, agitated, confused, or disoriented patients who receive mechanical ventilation; ventilator disconnections and extubations in patients with ARDS, for example, can abruptly precipitate life-threatening arrhythmias, hypoxemia, asphyxia, or aspiration. Special caution is warranted for orally intubated patients who tend to self-extubate more readily (see Chapter 6). In the setting of acute pulmonary edema, the interruption of PEEP for even brief periods (suctioning, tubing changes, etc.) may cause profound, slowly reversing desaturation as lung volume falls and the airways rapidly flood with edema fluid. The stomach should be actively decompressed in most patients with air swallowing, vomiting, or ileus. For mechanically ventilated patients, the clinician must stay alert to the possibility of tension pneumothorax, especially in patients with radiographic evidence of pneumomediastinum or subcutaneous emphysema (see Chapter 8).

Consider ARDS to Be a Multisystem Disease

Intravascular volume must be regulated carefully (see following). Although fluid excess must be avoided to minimize lung water and improve oxygen exchange, severe fluid restriction may compromise the perfusion of the gut and kidney. Appropriate levels of nutritional support and prophylaxis for deep venous thrombosis, skin breakdown, and gastric stress ulceration should be considered for all mechanically ventilated or immobile patients (see Chapter 18). The routine early use of corticosteroids is not justified. Adverse changes in immunity, mental status, metabolism, and protein wastage tend to outweigh any potential therapeutic benefit in the first week of the course. However, ARDS-like illnesses caused by documented vasculitis, fat embolism, or allergic reaction are exceptions to this rule. Corticosteroids may be of extreme benefit in certain steroid-responsive diseases that mimic ARDS (e.g., bronchiolitis obliterans organizing pneumonia [BOOP], pulmonary hemorrhage syndromes, Pneumocystis carinii pneumonia). Moreover, in such life-threatening circumstances, relative adrenal insufficiency occasionally occurs; if the presentation is compatible, this problem should be pursued diagnostically and stress doses of hydrocortisone given (see Chapter 32). When used in sufficient doses and for appropriate durations, corticosteroids may help resolve the fibroproliferative stage of this illness. Although there is no firm consensus on whether corticosteroids improve eventual mortality, it is clear from the large ARDSNet trial that steroids help free many patients from ventilator support more quickly. Despite many attempts to find an effective anti-inflammatory pharmaceutical approach, there remains little unequivocal confirmation from clinical trials of predictable benefit from any tested medication. The imprecision of the consensus definitions for ARDS may partially explain this failure.

Improving Tissue Oxygen Delivery

In the setting of ALI/ARDS, attention focuses on maintaining an adequate oxygen delivery/consumption ratio while reversing the underlying lung pathology. Oxygen delivery is the product of cardiac output and the $O_2$ content of each milliliter of arterial blood. Techniques for improving cardiac output are discussed in detail in Chapter 3. The $O_2$-carrying capacity can be improved by increasing Hgb concentration and optimizing its dissociation characteristics. Increasing Hgb tends to increase mixed venous oxygen saturation as it reduces the
need for any rise in cardiac output compensatory to anemia. Both of these actions (lower cardiac output demand and higher mixed S\(\text{v}\) with bar above\(\text{O}_2\)) tend to reduce venous admixture. As hemoglobin concentration rises, blood viscosity increases, retarding passage of erythrocytes through capillary networks. Therefore, actual \(\text{O}_2\) delivery can be impaired as hematocrit (Hct) rises. Although the optimal target for patients experiencing an oxygenation crisis is unknown, it makes sense to restore Hgb concentration to approximately 8 to 10 g/dL. More extensive supplementation increases the risks of transfusion without proven benefit (see Chapter 14).

**FIGURE 24-8. Schema for managing hemodynamic failure in ARDS based on the monitoring of respiratory pulse pressure variation as an indicator of fluid responsiveness.**

Because extravascular water accumulates readily in the setting of permeability edema, fluids should be used judiciously to keep the lungs from flooding and to discourage water retention, consistent with adequate oxygen delivery (Fig. 24-8). The results of a well-designed and conducted large ARDSNet trial strongly support the superiority of a “dry lung” approach, as ventilator and ICU days were fewer than experienced with a fluid-liberal strategy. Careful use of inotropes and other vasoactive drugs can help to avoid volume excess, especially in certain postoperative or posttrauma settings. Driving the cardiac output to “supraphysiologic” levels, however, is not routinely helpful for medical patients with ARDS.
**Oxygen Therapy**

Increasing the FiO\textsubscript{2} improves PaO\textsubscript{2} in all instances in which shunting is not entirely responsible for desaturation. The goal is to increase arterial O\textsubscript{2} saturation to 87% to 95% without risking O\textsubscript{2} toxicity. Hyperoxia (arterial saturations >98%) may cause vasoconstriction in vital organs and should be avoided. As a rule, very high inspired fractions of oxygen can be used safely for brief periods as efforts are made to reverse the precipitating cause. However, pulmonary oxygen toxicity, which is both concentration and time dependent, may be a greater risk than generally appreciated. High oxygen concentrations, which act in experimental models as a cofactor for VILI, independently result in inflammatory changes and eventual fibrosis. Moreover, when hypoxemia results from shunt, raising FiO\textsubscript{2} is ineffective. It seems logical, therefore, that efforts are made to reduce FiO\textsubscript{2} during the support phase of ALI, lower than 0.7 whenever possible.

**PEEP, Positioning, and Inspiratory Time**

PEEP, nonconventional modes, and other techniques intended to increase mean alveolar pressure often succeed in maintaining lung volume recruitment. These topics are reviewed in detail in Chapter 9. Virtually all patients (with or without lung injury) benefit from low levels of PEEP (e.g., 5 cm H\textsubscript{2}O), which helps compensate for the loss of volume that accompanies recumbency and translaryngeal intubation. Although PEEP inhibits airway flooding, discourages migration of airspace biofluids, improves PaO\textsubscript{2}/FiO\textsubscript{2}, and can be shown experimentally to reduce VILI for the same plateau pressure, there is little clinical evidence that high PEEP independently protects against or helps resolve ARDS. PEEP increases the number of patent alveoli and therefore may help restore surfactant synthesis, but it also distends already functioning alveoli, potentially increasing overall mechanical strain within the lung. Although PEEP may be effective in the relaxed subject, its volumerecruiting effects can be negated by patient effort. Vigorous expiratory muscle action forces the chest to a lung volume lower than the PEEP-appropriate equilibrium position. When this happens, relaxing or silencing the expiratory muscles by sedation (and/or paralysis, if needed) can prove helpful in improving oxygenation. When infiltration is highly asymmetrical, increases of PEEP may be ineffective or even counterproductive. When one lung is affected differentially, oxygenation occasionally improves—sometimes dramatically—with the good lung in the dependent position, but this is not observed reliably. Again, care should be taken to ensure that secretions from the infiltrated lung are not transferred into the airway of the dependent and initially viable lung during this process. As discussed later and in Chapter 9, shifts from the supine to the prone position often help dramatically in reversing hypoxemia in the early stage of ARDS.

**Recruiting Maneuvers and PEEP Selection**

The principles of avoiding VILI are discussed in Chapter 8. Assuming that peak inflation pressure does not rise simultaneously, applying PEEP alone does little to recruit atelectatic lung units but only keeps recruited units from recollapsing. To accomplish optimal recruitment (and thereby improve oxygenation and reduce potentially damaging lung stresses), sufficient pressure must first be applied to exceed the opening pressures of most recruitable units and then to maintain a total PEEP sufficient to exceed their closing pressures (Fig. 24-9). Brief applications of high airway pressure do not cause VILI, especially when achieved by elevating PEEP with a fixed and modest driving pressure. Recruitment maneuvers are rational for PEEP selection (the “decremental” approach) when potentially hazardous tidal plateau pressures (>25 cm H\textsubscript{2}O) are needed to maintain ventilation. “Recruiting” maneuvers with relatively high pressure also may be required after airway suctioning, following brief disconnections of the ventilator circuit, or periodically to achieve and sustain optimal arterial oxygenation when small tidal volumes are used for patients with acute oxygenation failure, as they often are in ARDS. Methods for accomplishing lung recruitment and selecting PEEP are described in Chapter 9.
Secretion Management and Bronchodilation

Although ARDS is generally regarded as a problem of parenchymal injury, airway edema and secretion retention may contribute to hypoxemia, especially in “primary” ARDS. Retained secretions often pose an overlooked problem that increases endotracheal tube resistance, infection risk, hazard of barotrauma, and the maldistribution of ventilation. Furthermore, for some patients with diffuse lung injury, profound bradycardia develops during ventilator disconnections and/or airway suctioning. Although hypoxemia occasionally contributes, this bradycardia usually is reflex in nature and responds to prophylactic (parenteral) atropine or prompt reapplication of positive airway pressure. The now ubiquitous closed circuits that do not interrupt tidal breath delivery or PEEP during suctioning help avert these episodes.

Importance of Reducing Oxygen and Ventilation Requirements

Lung-protective ventilation strategies usually focus on the “supply side” components of the tidal cycle—tidal volume, plateau pressure, driving pressure, and PEEP. Much less clinical attention has been directed toward the “demand” side of the equation, that is, at reducing the need to apply potentially damaging airway pressures and to push high vascular flows through the damaged lung. The drivers of these needs are minute ventilation and cardiac output. Both are potentially modifiable, and doing so in the first days of ALI/ARDS may dramatically reduce the iatrogenic potential of ventilatory support.

Fever, agitation, overfeeding, vigorous respiratory activity, shivering, sepsis, and a host of other commonly
observed clinical conditions can markedly increase VO$_2$, the need for O$_2$ delivery, and the extent of mixed venous and arterial O$_2$ desaturation. Shivering must be prevented during fever reduction. Sedation and the use of antipyretics in preference to cooling blankets often make good therapeutic sense. (Although phenothiazines may prevent shivering, their use may inhibit the cutaneous vasodilation necessary for rapid heat loss.) When possible, correction of metabolic acidosis reduces the ventilation need.

Enforced acceptance of respiratory acidosis (and of a lower V$_{E}$)—“permissive hypercapnia”—can be achieved in the ventilated patient by suppressing the drive to breathe and/or by preventing contraction of the respiratory muscles. A good argument can be made to encourage gentle, spontaneous efforts whenever feasible to do so. Nonetheless, for the first 24 to 48 hours of treatment, deep sedation, coupled with pharmacoparalysis if necessary, represents a valuable intervention to reduce oxygen consumption and improve PaO$_2$ in patients who are severely ill, remain agitated, or fight the ventilator despite more conservative measures. It is prudent to target lower minute ventilation in the first days of ARDS therapy when the lung is most recruitable and at risk for VILI (Table 24-3). Although paralysis is often helpful during this initial period of machine support, protracted paralysis must be avoided for several reasons. Paralysis places the entire responsibility of achieving adequate oxygenation and ventilation on the medical team. Furthermore, the patient is defenseless in the event of an unobserved ventilator disconnection. Paralysis also silences the coughing mechanism and creates a monotonous breathing pattern that encourages secretion retention in dependent regions. Finally, protracted and unmonitored paralysis may cause weakness or devastating neuromyopathy (see Chapter 17).

**Mechanical Ventilation of Acute Lung Injury and ARDS**

**Traditional Approach**

The basic principles of managing ARDS are widely accepted. The primary objective is to accomplish effective gas exchange without imposing iatrogenic damage by inspired oxygen or airway pressure. Nonetheless, although the principles of VILI prevention are increasingly well understood (see Chapter 8), knowledge remains incomplete. Moreover, the relative hazards of oxygen therapy, high-pressure ventilatory patterns, and abnormal target values for arterial blood gases, pH, and cardiac output are still actively debated (Table 24-4).

<table>
<thead>
<tr>
<th>Table 24-3. Conditionally$^a$ Important to VILI During High-Stress Ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• PaCO$_2$ and pH</td>
</tr>
<tr>
<td>• Frequency</td>
</tr>
<tr>
<td>• Position</td>
</tr>
<tr>
<td>• Vascular pressures</td>
</tr>
<tr>
<td>• Temperature</td>
</tr>
<tr>
<td>• Minute ventilation and flow</td>
</tr>
<tr>
<td>• Energy load and ventilatory power</td>
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</table>

$^a$In the presence of high mechanical stresses.
Most traditional ventilatory strategies used in intensive care evolved directly from anesthetic and surgical postoperative practices. When the lungs are uninjured and their capacity to expand remains normal (as is common in the perioperative period), large tidal volumes \( (V_T) \) of 12 to 15 mL/kg generate only modest end-inspiratory transalveolar pressures and require acceptably low driving pressures because compliance, the variable that determines the required driving pressure, remains good. In fact, large tidal volumes prevent the microatelectasis that accompanies monotonous shallow breathing and are needed by many spontaneously breathing patients to satisfy high ventilatory demands (e.g., metabolic acidosis) or maintain comfort.

Postoperatively, the mandatory respiratory rate usually is adjusted to “normalize” pH and/or PaCO\(_2\), and sufficient PEEP is used to achieve acceptable O\(_2\) delivery at what is assumed to be a toxic FiO\(_2\). (An FiO\(_2\) < 0.70 is commonly targeted.) Until the last decades, airway pressures have been monitored but not rigidly constrained.

### Table 24-5. Characteristics of Early- and Late-Phase ARDS

<table>
<thead>
<tr>
<th></th>
<th>Early Phase (0-3 Days)</th>
<th>Late Phase (&gt;7 Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural collagen</td>
<td>Strong</td>
<td>Degraded</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>Prevalent</td>
<td>Less prevalent</td>
</tr>
<tr>
<td>Edema</td>
<td>Prevalent</td>
<td>Less prevalent</td>
</tr>
<tr>
<td>Mechanical stresses</td>
<td>Heterogeneous/recruitable</td>
<td>Heterogeneous/less recruitable</td>
</tr>
<tr>
<td>Ventilator lung injury</td>
<td>Edema, inflammation and hemorrhage</td>
<td>Predisposition to barotrauma</td>
</tr>
</tbody>
</table>
ARDS, acute respiratory distress syndrome.

With few modifications, this high tidal volume, normoxic, normocapnic ventilation paradigm was initially adopted as the standard approach for supporting most critically ill patients as well. Consequently, tidal volumes that exceed 800 mL and end-tidal (plateau) alveolar pressures approaching 50 cm H$_2$O—values that seriously violate currently understood principles of lung protection—were accepted in decades past when needed to normalize blood gases. How best to select “optimal” PEEP remains controversial, and machine settings that achieve all important clinical objectives do not invariably coincide. A growing number of practitioners are now shifting first priority from gas exchange and oxygen delivery to a strategy that minimizes the potentially injurious effects of mechanical ventilation.

Ventilator-Induced Lung Damage

Implications of Evolving Histology

Histologic findings evolve continuously (but heterogeneously) over the course of ALI (Table 24-5). It is reasonable to assume that all lung regions sustain the initial insult more or less simultaneously and that, in the most severe cases, proliferation, organization, remodeling, and fibrosis sequentially follow an initial phase of edema, atelectasis, and relatively high recruitability that later declines. Although parenchymal damage is widespread, the nature, severity, pace of evolution, and perhaps even the stage of injury vary from site to site within the damaged lung. Early in the course of ARDS, gravitationally dependent areas have the least transpulmonary pressures and therefore are extensively consolidated and atelectatic, whereas nondependent regions tend to aerate best. Regional blood flows and vascular pressures also vary (Fig. 24-6). Changes of body position reshape the lung and chest wall, influence radiographic and CT findings, and affect gas exchange. Although counterexamples occasionally occur, perhaps 60% to 70% of patients respond to prone positioning by improving PaO$_2$ significantly during this early phase of ARDS (see later). The efficacy of PEEP in improving oxygen exchange relates directly to the reversal of atelectasis and the redistribution of lung water. It is not surprising, therefore, that recruitability and PEEP’s effectiveness in improving oxygen exchange tend to decline as time passes. Although initially a large proportion of the edematous and atelectatic lung can be aerated if sufficient pressure is used, recent studies suggest that only a small percentage of the infiltrated lung remains so after the first few days of ARDS onset.

Table 24-6. Modifiable Determinants of VILI

| Translung (alveolar) pressure |
| Tidal volume |
| PEEP |
| Body position |
| Driving pressure ($V_T/C = |P_{plateau} - PEEP_{total}|$) |
| Minute ventilation and inspiratory flow rate |
| Conditional cofactors |
| - Vascular pressures and flows |
| - Body temperature |
| - Airway spread of inflammatory edema (propagation) |
The collagen framework of the normal lung remains relatively intact during the initial injury period but later weakens as inflammation gradually degrades the structural protein and nonuniformly remodels the lung's architecture. Therefore, the same pressures that were withstood initially may cause alveolar disruption after the disease is well established. This may explain the tendency for radiographically detectable barotrauma to occur late in the course of the disease—often well after gas exchange abnormalities have noticeably improved and ventilatory pressures have declined.

**Tidal Volume, PEEP, Driving Pressure, and VILI (See Chapters 5 and 8) (Table 24-6)**

Only a portion of the lung remains accessible to gas after injury; in severe cases, no more than one third of all alveoli are patent. Considering that well-ventilated lung units may retain nearly normal elastance and fragility, the apparent “stiffness” of the lung in the early phase of ALI is better explained by fewer functioning alveoli than by a generalized increase in recoil tension. Increased tissue recoil contributes more significantly later on, when cellular infiltration is intense, edema has been reabsorbed or organized, atelectasis is less extensive, and fibrosis is under way. In any given individual, raising tidal volume obligates higher inflating pressure. One cannot say, however, that a given tidal volume is safe or dangerous until it is known what pressure it generates and that depends on the capacity of aeratable lung tissue—an inverse function of disease severity.

**IMPORTANCE OF EARLY-PHASE MANAGEMENT TO VILI AVOIDANCE**

The first hours of ventilation management may determine the eventual outcome. In the earliest phase, the injured lungs are edematous, relatively recruitable, and collapsible. Reaeration at this stage may help prevent surfactant depletion, improve mechanical homogeneity, and avoid the inadvertent application of damaging forces at points of stress focusing. Such considerations are the primary motivation behind the “open lung” approach, which seeks to apply adequately high end-expiratory and mean airway pressures by a variety of techniques so as to improve the aeratable capacity and prevent tidal cycles of opening and collapse. The key is to intervene early, so that damaging forces are avoided from the outset. Waiting too long may shrink the functioning “baby lung” and set into motion a dangerous cycle of progressive iatrogenic VILI. Prone positioning and avoidance of vigorous spontaneous efforts should be early considerations (Fig. 24-10).

Although prone positioning can be thought as part of an open lung approach, what value such open lung modes as APRV or HFO offer beyond conventional lung protection remains to be convincingly shown (see Chapters 5 and 8).
Tissue Stresses Caused by Lung Inflation

Because the lung's reduced functional compartment must accommodate the entire tidal volume, large (traditional) tidal volumes may cause end-inspiratory overdistension, local hyperventilation, and inhibition or depletion of surfactant. Moreover, during repeated and abrupt inflations to high transalveolar pressures, intense shearing forces may develop at the junctions of structures that are mobile (aerated lung units) with those that are immobile, collapsed or consolidated alveoli, and distal conducting airways (see Chapter 8). Such stress focusing can markedly amplify the damaging effects of a given transalveolar pressure, providing a good rationale for trying to keep the lung well recruited and the peak transalveolar forces (alveolar minus pleural) low and homogeneously distributed. It is recommended that tidal volumes are kept within the range of 4 to 8 mL/kg predicted body weight, depending on the PEEP used and the resulting plateau and driving pressures measured at the airway opening. When the chest wall is normal and breathing is passive, these should not exceed 30 cm H₂O and 15 cm H₂O, respectively.
Tidal pressures across the alveolus must neither rise too high at any time during the disease course nor fall too low, especially during the first 3 to 5 days of treatment. Structural (tearing, ripping, etc.) damage to the parenchyma and more subtle mechanical signaling of inflammation have been shown to result from high alveolar and driving pressures, especially when flow rate is high. The airway inflation pressures are not the stretching pressure that correlates with VILI; instead, transalveolar pressures (roughly approximated by the difference between alveolar and pleural pressures) are the relevant variables. Vigorously breathing patients often contribute markedly to the transalveolar pressures. Such pressure contributions can be estimated using an esophageal balloon catheter to estimate pleural pressure changes (see Chapters 5 and 8).

When ventilation is passive, the plateau pressure is perhaps the best clinical correlate of peak alveolar (but not necessarily transalveolar) pressure. The severity of “stretch injury” seems greatest when these maximum transalveolar pressures are high and insufficient PEEP fails to keep unstable lung units fully recruited. The difference between endinspiratory (plateau) and end-expiratory alveolar pressures, equal to $V_T/C$ and known as the “driving pressure,” is perhaps the most important feature of the tidal cycle that correlates with mortality risk (Fig. 24-11). Without sufficient PEEP, unstable and collapsible alveoli may wink open and close with every tidal cycle, generating shearing stresses within junctional tissues and helping to deplete surfactant. Increases in cycling frequency and duration of exposure to adverse ventilatory patterns accentuate any tendency for damage. The magnitude of blood flow in these stressed areas also may play an important role.

**Driving Power and the Importance of Cycling Frequency** *(Table 24-7)*

At levels of minute ventilation and tidal volume that are traditionally accepted, the ventilator may cycle in excess of 30,000 times per day (20 cycles/min, 60 min/h, 24 h/day). Even if each tidal pressure profile is only slightly
damaging, the cumulative effect might be severe. It is very important to reduce $V_E$ requirements and cycling frequency whenever high cycling pressures are in use. Raised frequency is much less damaging when tidal parenchymal stresses remain within acceptable bounds, as exemplified by high-frequency ventilation applied at modest mean airway pressures (HFV). Once a threshold for plateau pressure is exceeded, however, the driving power (the product of driving pressure and minute ventilation) provides an attractive unifying concept that takes both driving pressure per cycle and frequency into account, attributing damage to the rate that high strain mechanical energy is delivered to the parenchyma per unit time. It follows that although the characteristics of the tidal cycle are crucial, minute ventilation is also of great importance. As our understanding of VILI has evolved, perhaps even closer than power to the root cause of inflation-caused damage is the intense application of excessive tidal strain (Fig. 24-12) (see Chapter 8).

Table 24-7. Potential Importance of Oxygen Demand for VILI Expression

<table>
<thead>
<tr>
<th>Potential Importance of Oxygen Demand for VILI Expression</th>
</tr>
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<tbody>
<tr>
<td>- Cardiac output</td>
</tr>
<tr>
<td>- Pulmonary blood flow</td>
</tr>
<tr>
<td>o Microvascular pressure gradient</td>
</tr>
<tr>
<td>- Ventilation requirement and power</td>
</tr>
<tr>
<td>- Cycling frequency</td>
</tr>
<tr>
<td>- Ventilation pressures</td>
</tr>
<tr>
<td>o Static</td>
</tr>
<tr>
<td>o Dynamic</td>
</tr>
</tbody>
</table>

![Figure 24-12](image.png)

**FIGURE 24-12. Evolving concepts in the lung-protective approach to ventilation.** Modifying the characteristics of the individual tidal cycle logically must be complemented by restraint of cycling frequency and minute ventilation.

*Choice of PEEP (See Chapter 9)*
Although it is now widely recognized that chest wall compliance differences, spontaneous efforts, and inherent variability in the aeratable capacity of the lung to accept volume invalidate firm numerical guidelines for PEEP or tidal volume selection, the often discussed and empirically derived pressure-volume display may fare little better. As a composite of the behaviors of all alveoli within the heterogeneous lung, the contours of the static pressure-volume loop (comprised of two quite different inspiratory and expiratory limbs) (Fig. 24-13) obscure very important regional differences. Alveoli in dependent regions are most susceptible to collapse, and those in nondependent regions are vulnerable to overdistension. This variability of opening pressures helps account for the zones (rather than points) of lower and upper inflection. In fact, as detailed in Chapter 9, recruitment and overdistension coexist at virtually all lung volumes across the inspiratory capacity range. The proportions of each are likely to account for such topographical features of the passive inflation curve as the lower inflection point \((P_{flex})\), which is no longer considered a theoretically valid guide to PEEP selection. Nonetheless, early clinical trials demonstrated better outcomes in the group using \(P_{flex}\) to guide PEEP selection than those assigned to traditional (least PEEP for acceptable \(\text{PaO}_2/\text{FiO}_2\)). At present, an empirical approach that incorporates a recruitment maneuver and one or more of multiple indicators of response to PEEP set decrementally (e.g., minimized driving pressure during volume control) appears most rational (see Chapter 9). Published clinical trials conflict, but perhaps the majority indicate improved outcomes for ventilating strategies geared to avert widespread alveolar collapse during tidal breathing while keeping the plateau pressure beneath a ceiling of approximately 30 cm H\(_2\)O. That is not to say that all patients should be ventilated with high PEEP, especially not those who have low plateau pressures and adequate oxygenation, but many severely ill patients will need initial PEEP levels \(\geq 12\) to 15 cm H\(_2\)O to keep most recruitable alveoli open. High PEEP requirements are also needed to open the normal lungs of the massively obese. Even patients with normal lungs and chest walls require 5 to 10 cm H\(_2\)O PEEP simply to offset the functional residual capacity (FRC) reduction that occurs with recumbency.
FIGURE 24-13. Pressure-volume curves of the respiratory system in the earlier and later stages of ARDS. In the earlier stage of ARDS, distinct lower and upper inflection zones are evident, and the hysteresis (H) between inspiratory and expiratory limbs is prominent. Later, the inflection zones are less well demarcated, and hysteresis is reduced. ARDS, acute respiratory distress syndrome.

**Implications of Pressure Limitation for Tidal Volume**

Based on the results from the influential NIH-sponsored trial of tidal volumes, a reasonable starting tidal volume target for patients with ARDS is 6 mL/kg of lean body weight. However, this rather arbitrary value may not suit all patients because of comfort issues, high-ventilation requirements, oxygenation concerns, or pressure limitations imposed by a very small aeratable capacity of severe ARDS ("baby lung"). Therefore, $V_T$ should be adjusted with guidance by plateau pressure, driving pressure, and the response of oxygen exchange to changes of tidal volume.

**Modes of Mechanical Ventilation in ARDS**

Many choices are equivalent, as long as the practitioner ensures adequate $O_2$ delivery at a safe $FiO_2$, follows similar guidelines for lung protection, and remains alert to the potential shortcomings and complications of the mode in use. Delivery of conditioned oxygen by high-flow nasal cannula (HFNC) or noninvasive ventilation by a well-selected interface may allow some alert and well-conditioned patients with mild to moderate ARDS to avoid intubation altogether, assuming the cause has been effectively treated. The majority of ARDS patients, however, are not so fortunate. Reflex drives to breathe increase the frequency and depth of tidal breaths, risking self-inflicted overstretch injury to the lung. This hazard is accentuated when the mask imposes significant dead space, a characteristic of most such interfaces. The fact that the patient with ARDS has the reduced ventilating capacity of the baby lung means that any added $CO_2$-eliminating burden will be met with a nonlinear increase in
ventilatory effort—a particular concern for recently extubated patients and for those being weaned from ECMO. In other words, noninvasive mask interface selection may prove key to success or failure. As a rule, for the majority of ARDS patients who require intubation, spontaneous efforts should be encouraged only if gentle. Gentle spontaneous breathing is seldom the case in the initial 24 to 48 hours of full-blown ARDS. In those who breathe vigorously, airway pressure-targeted modes (such as pressurecontrolled or pressure-supported ventilation) leave the transalveolar pressures unregulated. Note that volume control ventilation, where tidal volume is preset, does not guarantee that damaging stresses are not being applied to certain lung regions. Therefore, when oxygenation remains marginal, heart function is seriously compromised, or ventilatory efforts continue to be labored, and suppressing such activity seems to be the prudent course.

It has been argued that techniques such as pressure control, high-frequency oscillation, pressureregulated volume control, inverse ratio ventilation, and airway pressure release ventilation (APRV) confer advantages over the more traditional approaches, but none has yet been shown in a fair comparison to be consistently superior to its alternatives. Conversely, when misused, all can be dangerous. The general concepts of effective and safe “lungprotective” ventilation are outlined elsewhere and apply to most (if not all) intubated patients (see Chapters 7 and 8). The important difference in managing patients with ARDS is that the stakes are higher; choices of maximum allowed tidal pressure and chosen level of PEEP may be crucial to ensure safe ventilatory support of the mechanically heterogeneous lung. What is often forgotten is the need to reduce unnecessary ventilation and oxygenation requirements to reduce the patient's need to be exposed to high-pressure breathing cycles.

Permissive Hypercapnia
Carbon dioxide retention is often an inevitable consequence of a lung-protective strategy that tightly restricts applied pressure and maintains a certain minimum (end-expiratory) lung volume (see Chapter 7). Maintaining normocapnia increases physiologic dead space of the small functional baby lung and is not appropriate if the cost is impaired lung healing and heightened risk of extending tissue damage. Using lower tidal volumes and minute ventilation often obligates CO$_2$ retention. “Permissive hypercapnia,” a strategy that allows alveolar ventilation and peak ventilatory pressures to fall and PaCO$_2$ to rise, may reduce barotrauma, limit dead space, and enhance survival in status asthmaticus and ARDS. Although VILI is likely to be less, the basis for the survival advantage of the lung-protective approach has not yet been clearly determined. However, lungs damaged by stretch injury are susceptible to pneumonia and may be a source of inflammatory mediators that are transferred to the systemic circulation to incite dysfunction elsewhere. Disruption of the lung's architecture also may promote bacteremia or even gas microembolism. Apart from reducing the need for the lung to undergo damaging stress and strain, acute hypercapnia holds the potential for reducing oxidative injury—a protective effect of respiratory acidosis. Despite these advantages, acute hypercarbia raises concerns as well.

PHYSIOLOGIC EFFECTS OF HYPERCARBIA
The physiologic effects of CO$_2$ retention are determined by the severity of hypercapnia and the rate of its buildup (Table 24-8). Except in the most severe cases or those complicated by extraordinary CO$_2$ production, the CO$_2$ retention that results from the pressure-targeted ventilation itself is usually modest (PaCO$_2$ < 70 mm Hg). Chronic hypercapnia of this magnitude seems to have few notable side effects, other than the reduction in ventilatory drive attendant to compensatory metabolic alkalosis. Respiratory acidosis may even reduce the intensity of inflammation or limit the expression of VILI.

Although gradual elevations of PaCO$_2$ (2- to 5-mm Hg increases per hour) are often tolerated remarkably well, abrupt increases are ill advised. Acute elevations in PaCO$_2$ not only promote dyspnea but also increase
sympathetic activity, raise cardiac output, heighten pulmonary vascular resistance, alter bronchomotor tone, impair skeletal muscle function, dilate cerebral vessels, and impair central nervous system function. Allowing hypercapnia may not be a viable option for all patients with ALI (e.g., patients with coexisting head injury, recent cerebral vascular accident, or significant cardiovascular dysfunction [Table 24-9]). Carbon dioxide retention may be tolerated poorly by patients with autonomic insufficiency, \( \beta \)-blockade, or other conditions interfering with sympathetic tone and compensatory mechanisms.

### Table 24-8. Consequences of Hypercapnia

<table>
<thead>
<tr>
<th>System</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Reduced alveolar PO(_2)</td>
</tr>
<tr>
<td></td>
<td>Rightward shift of Oxy-Hgb curve</td>
</tr>
<tr>
<td></td>
<td>Impaired diaphragm function</td>
</tr>
<tr>
<td></td>
<td>Pulmonary vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>Worsened ([V with dot above]/[Q with dot above]) mismatching</td>
</tr>
<tr>
<td>Renal</td>
<td>Enhanced bicarbonate reabsorption</td>
</tr>
<tr>
<td>CNS</td>
<td>Cerebral vasodilation</td>
</tr>
<tr>
<td></td>
<td>Increased intracranial pressure</td>
</tr>
<tr>
<td></td>
<td>Depressed consciousness</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Reduced cardiac contractility(^b)</td>
</tr>
<tr>
<td></td>
<td>Stimulation of sympathetic-adrenal axis</td>
</tr>
<tr>
<td></td>
<td>Pulmonary vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>Lower systemic vascular resistance</td>
</tr>
</tbody>
</table>

\(^a\) Most effects wane with time as cellular and extracellular pH readjust.

\(^b\) Only if not offset by adrenergic reflex compensation.

### Table 24-9. Cautions and Contraindications to Permissive Hypercapnia\(^a\)

<table>
<thead>
<tr>
<th>Intracranial hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head trauma</td>
</tr>
<tr>
<td>Hemorrhage</td>
</tr>
<tr>
<td>Severe systemic hypertension</td>
</tr>
<tr>
<td>Space-occupying lesions</td>
</tr>
</tbody>
</table>

| Cardiovascular instability |
When ventilation changes are made quickly, arterial pH may not closely reflect the pH of the intracellular environment in which key cellular enzymes operate. The magnitude of any intracellular acidosis resulting from permissive hypercapnia, however, is almost certain to be less than the profound intracellular pH changes produced by ischemia. Because PCO$_2$ affects cardiac output and influences vascular and bronchomotor tone, it is uncertain if hypercapnia disturbs $[\text{V with dot above}]/[\text{Q with dot above}]$ matching or modulates the extent of lung injury and edema during the course of mechanical ventilatory support. Initially, the implementation of permissive hypercapnia often requires deep sedation and/or paralysis, a requirement that helps reduce ventilation demand but may eventually be associated with serious side effects: impaired secretion clearance, fluid retention, residual muscle weakness, and delirium. Moreover, permissive hypercapnia may not be advisable (or even possible to implement safely) in the setting of a coexisting metabolic acidosis or an uncorrected hypoxemia.

**Alternative Ventilatory Strategies and Adjuncts to ARDS Ventilation**

Interest continues in devising ways in which to accomplish effective arterial oxygenation and ventilation without inflicting further damage on the injured lung. Some of these innovations modify the fundamental nature of ventilatory support, whereas others provide gas exchange external to the lungs (extracorporeal gas exchange), alter body position (prone positioning), or administer therapeutic agents designed to aid $[\text{V with dot above}]/[\text{Q with dot above}]$ matching (nitric oxide, aerosolized prostacyclin, etc.). One technique, now abandoned, modified the nature of the gas-carrying medium itself (partial liquid ventilation with perfluorocarbon). A few of these adjuncts are at the margin or just beyond the perimeter of routine clinical practice.

**High-Frequency Ventilation**

In its various forms, HFV has been investigated and clinically applied for more than three decades. Such attention is understandable; when conducted at an appropriate lung volume and frequency, HFV seems well aligned with current principles of lung protection and has a clear rationale (see Chapter 7). Very small tidal volumes (believed in most instances to be <200 mL) have the potential to confine the maximum alveolar and driving pressures to the ranges thought prudent, and inherently high end-expiratory pressures tend to prevent widespread collapse of unstable tissues. Moreover, with the advent of effective adult oscillators, implementation of HFV became a viable option for clinical application in ARDS. Deep sedation, need for careful and continuing bedside surveillance, hemodynamic stresses associated with high mean airway pressures, and difficult and imprecise monitoring have been barriers to its adoption into adult practice. Early published experience using HFO as a salvage technique for ARDS patients failing more conventional approaches appeared quite favorable and suggested that this approach might be advisable at a much earlier point in the life-support process. Unfortunately, two influential clinical trials not only failed to confirm its superiority over a lung-protective conventional approach but demonstrated the potential for HFO operating at high mean airway pressures to inflict greater overall harm than conventional lung-protective approaches. Given the difficulties posed in its

<table>
<thead>
<tr>
<th>Cor pulmonale (severe)</th>
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<tbody>
<tr>
<td>β-Blockade</td>
</tr>
<tr>
<td>Severe, uncorrected metabolic acidosis</td>
</tr>
</tbody>
</table>

$^a$Accentuated by rapid rise of PaCO$_2$. 
implementation, such results have discouraged HFO use in current adult practice.

**Extrapulmonary Gas Exchange**

Partial substitution for the lung’s gas exchanging function reduces the requirement for ventilating pressure and aids in oxygenating the arterial blood. Until quite recently, extrapulmonary gas exchange held diminishing appeal given that that strategies for lung protection are widespread and acceptance of abnormal blood gas tensions is increasingly implemented. Nonetheless, associated risks for the critically ill—though still quite significant—have declined as advancing technology improved catheters and gas exchanging surfaces, anticoagulation requirements declined, and the devices themselves became more portable and user-friendly. As shown in the H1N1 influenza epidemic, ECMO may provide an effective option for those who otherwise have only a slim hope of survival. Methods for assisting in the process of exchanging respiratory gases include extracorporeal membrane oxygenation (ECMO) and extracorporeal CO$_2$ removal (ECCO$_2$R) by pumpless arteriovenous and pump-assisted venovenous methods (Fig. 24-14). All are highly technical methods best undertaken by an experienced and dedicated team. Each has a good rationale for the appropriate indication, and laboratory experience and various clinical reports have been encouraging. Early implementation of ECCO$_2$R makes particularly good sense when demands are high and/or optimized and lung-protective conventional approaches with ventilation, sedation, and prone positioning appear to be failing.

**FIGURE 24-14. Extracorporeal CO$_2$ removal.** A limited amount of venous blood flowing through the gas exchanger can be purged free of nearly all the CO$_2$ it contains. In a sense, the exchanger is up to nine times more efficient than the normal lung in performing this task.
Much lower blood flows are needed to effectively remove CO\textsubscript{2} (e.g., approx. 1 L/min) than are needed to effectively support oxygenation (e.g., approx. 3 L/min). The physiologic reason is that the blood returning to the vena cava can be stripped entirely free of its CO\textsubscript{2} load, whereas the volume of oxygen added to the venous blood is limited by the constraints of the oxyhemoglobin dissociation curve. Because smaller catheters can be used and lower flows need to be diverted, ECCO\textsubscript{2}R (as opposed to ECMO) tends to be well tolerated hemodynamically. Consequently, ECCO\textsubscript{2}R can be used in a wide range of patients when ventilation is the primary problem. Adding a hemodiafiltration loop to the external circuit confers even broader potential. Although experience to date with these exotic techniques has been limited and uneven, developmental advances continue, and well-selected patients may benefit dramatically. Extracorporeal access can now be provided by relatively large catheters placed percutaneously, lower clotting risk has allowed less aggressive anticoagulation, and blood product needs are now markedly lower. In at least one center experienced in ECMO/ECCO\textsubscript{2}R technique, extracorporeal support has been continued for longer than a month in multiple patients, with ultimate survival. It appears that membrane oxygenation may be the only hope of salvage in patients who are the most difficult to oxygenate or safely ventilate. It must be emphasized that the risks and potential complications of extracorporeal gas exchange are serious and that a full understanding of its effects on the lung and systemic physiology of critically ill patients has not yet been achieved. How best to modify ventilatory support and to make transitions between ECMO/ECCO\textsubscript{2}R application and discontinuation are still being worked out.

**FIGURE 24-15. Tracheal gas insufflation (TGI).** CO\textsubscript{2}-laden gas that fills the central airways at end-expiration is recycled to the alveolus with the subsequent inspiration. Expiratory flushing of CO\textsubscript{2} from the central airway by fresh gas helps improve CO\textsubscript{2} elimination and reduces dead space. The effectiveness of TGI is reduced when a
high alveolar dead space lowers the end-expiratory tracheal CO$_2$ concentration but is enhanced when hypercapnia raises the concentration of CO$_2$ in the central airways during expiration.

**Tracheal Gas Insufflation**

A theoretical alternative to allowing extreme or rapidly developing hypercapnia or to using extrapulmonary techniques for gas exchange in ARDS is to enhance the efficiency of CO$_2$ elimination at low $V_T$ and cycling pressures by the tracheal insufflation of fresh gas during expiration (tracheal gas insufflation [TGI]) (Fig. 24-15). Only a modest flow of CO$_2$-free gas (6 to 10 L/min) is required. Moreover, fresh gas can be injected selectively during expiration through a channel within a specialized endotracheal tube wall without significantly impeding exhalation or raising the airway pressure significantly. This minimally invasive approach reduces the effective series (anatomic) dead space by bypassing the airway proximal to the carina during inspiration, by washing out the PCO$_2$ of this same region during expiration, or by both. Because much lower concentrations of CO$_2$ are delivered to the central airway as the lungs deflate, TGI loses its effectiveness when there is a large amount of alveolar (as opposed to anatomic and apparatus) dead space. ARDS is a typical example of such a condition. Conversely, hypercapnia boosts the expiratory CO$_2$ concentration within the trachea, improving the effectiveness of TGI. Though seldom used, TGI would appear well suited to serve as an adjunct to a pressure-targeted, lung-protective ventilatory support for ARDS because of its potential to moderate the rate and extent of CO$_2$ retention.

**Prone Positioning**

Frequent changes of body posture are integral to normal activity, but normal positional variation is forgone for lengthy periods in the bedridden, critically ill patient. By tradition, the patient is cared for in a supine orientation, which allows more direct eye contact with the caregivers, family, and visitors, as well as better access to the vascular system and vital structures, thereby facilitating nursing care. Furthermore, cardiopulmonary resuscitation must be conducted in the supine position. Despite those undeniable advantages, there is good reason to question our current practice of using only the supine orientation. A growing interest in therapeutic positioning has been stimulated by the consistent observation that the prone position improves oxygen exchange significantly in approximately 70% of patients treated in the early phase of ARDS, allowing the physician to reduce both FiO$_2$ and PEEP. This occurs primarily because ventilation of dorsal areas improves, whereas perfusion remains relatively unchanged after the turn (Fig. 24-16). Moreover, prone positioning confers a lung-protective advantage in experimental models of VILI because it evens the regional distribution of transpulmonary pressures, reducing the local overdistension and collapse associated with PEEP in the supine position. Regional driving pressures—higher in dependent zones when supine—are also more uniform (see Chapter 9) (Fig. 24-17).

Perhaps in part for these reasons, a large and influential French trial demonstrated an impressive survival advantage in patients with severe ARDS treated greater than 16 hours daily in the prone position early in their hospital course. Although four earlier clinical trials of proning in ARDS failed to show a consistent survival advantage for all patients of varying severity, proned patients in the most severely affected cohorts of each study fared impressively better. This benefit has also been reported for those at the highest risk for VILI and in those who experience improved CO$_2$ exchanging efficiency (suggesting recruitment) at first proning (Table 24-10). Airways serving the expansive dorsal regions generally are better drained in this position as well. Although helpful later on in removing the retained secretions, in the first 24 to 48 hours, proning carries the attendant potential for injury propagation as mobile inflammatory biofluid is encouraged to migrate to previously unaffected anterior zones. (Adequate PEEP may counter this tendency.)
FIGURE 24-16. The lung changes its regional distribution of expansion in response to gravitational forces and the changing shape of the lungs as they conform to the increased stiffness of the anterior chest wall in the prone position.

**Characteristics of Prone Positioning**

- Alters conformation of the lung
- Reduces gradient of trans-lung pressure
  - Airway pressures better reflect overall stress when prone
- Recruits and stabilizes atelectatic lung units
- Encourages mouthward migration of secretions
- Attenuates VILI risk
- Other
  - Improves lymph drainage (?)
  - Improves efficacy of inhalational therapy (?)

**PRACTICAL POINTS IN PRONE POSITIONING (TABLE 24-11)**

Although hemodynamic parameters tend to remain unchanged, hypotension, desaturation, and arrhythmias may occur during the process of turning from the supine to the prone position. These transient problems generally do not persist and can be minimized by using sedation, prior airway suctioning, and 100% oxygen during the maneuver. Continuous arterial pressure monitoring, electrocardiography, and pulse oximetry are strongly advised. Deep sedation and occasionally paralysis will be required to secure patient compliance. Attention also must be given to preserving the position and patency of intravascular lines and
endotracheal tubes during the turning process. Use of a soft (air-cushioned) bed is all but mandatory for comfort and to help avoid local excesses of pressure (e.g., at the knees). Pillows must be used to support the hips, pelvis, shoulders, and head. The eyes must be protected. Patients with tracheostomies present a particular challenge. On average, the chest wall stiffens but the compliance of the integrated respiratory system (lungs and chest wall) generally changes little in shifting to the prone position. This is variable, however; and volume-controlled ventilation is advised in the process. Tidal volume should be monitored (and adjusted if necessary) during pressure-controlled ventilation, because it is influenced by any position-related changes in system compliance. For similar reasons, a given level of PEEP may be more or less effective in one position versus the other, and repeat titration of PEEP is advised after the turn. Although the optimal frequency of supine-prone interconversions is not clear, in current practice, most experienced centers maintain the prone position for approximately 16 to 20 hours when it shows an oxygenation advantage and “flip” patients supine once daily for about 4 hours to allow cleanup, nursing care, catheter placement, and imaging studies. Supine repositioning allows certain nursing procedures (washing, line dressing changes, etc.) to be delivered and helps resolve facial edema. If well tolerated, prone repositioning should be continued for the first 48 to 72 hours and reevaluated for efficacy afterward. After the first 3 to 5 days of illness, proning efficacy begins to wane. Failure to significantly improve oxygenation or CO\textsubscript{2} eliminating efficiency \((\text{PaCO}\textsubscript{2}/\text{VE})\) signals that proning is no longer needed.

Table 24-10. Advantages of Prone Positioning in ARDS

- “Regional” PEEP in well-perfused dorsal zones
- Reduced gravitational gradient of pleural pressure
  - Improved V/Q matching
  - More even distribution of transalveolar pressure, stress, and strain
    - Peak, end-expiratory and driving pressures
- Improved airway drainage
- Reduced LLL compression
- Improved distribution of inhaled medications (?)
- Better venous/lymphatic drainage (?)

Table 24-11. Practical Points for Prone Positioning in ARDS

- Soft bed
- Secure endotracheal tube and all lines before transition
- Sedate and preoxygenate before turning
- Initiate or maintain volume control ventilation
- Volume-controlled ventilation during turn
- Monitor carefully during transitions
- Support shoulders and hips
- Adjust mode, PEEP, and tidal volume after positioning
- Protect eyes, facial areas
- Exercise special caution if bronchopleural fistula is present
- Flip briefly to supine one to three times daily as needed and tolerated
- Maintain prone position >16 h/d
**Inhaled Nitric Oxide and Prostacyclin**

Nitric oxide (NO) is a key biologic mediator of smooth muscle relaxation. When inhaled, NO has the therapeutic potential to dilate the pulmonary vasculature in well-ventilated regions, tending to reduce pulmonary hypertension and improve the matching of ventilation and perfusion in an unevenly damaged lung. Inhaled NO is only active locally, as it is quenched immediately on exposure to Hgb. Extremely low concentrations of NO achieve nearly full effect. The physiologic effects of NO in ARDS are highly variable—sometimes dramatic but often quite modest. No trial has yet shown a convincing benefit of inhaled NO regarding mortality, and from a logistical standpoint, NO delivery is somewhat cumbersome and expensive to implement. Thus, current enthusiasm is muted, and the eventual place of NO in the management of ARDS has not yet been settled. At present, it seems most likely to benefit those cases in which life-threatening hypoxemia or symptomatic pulmonary hypertension is refractory to other measures.

Vasodilating aerosols, of which inhaled prostacyclin (e.g., epoprostenol or Flolan) is the most frequently used, operate by the same principle of selectively increasing perfusion to well-ventilated regions and appear to offer similar efficacy. Delivery and monitoring of inhaled prostacyclin are less complicated than NO, and expense is considerably less. Like NO, it is best viewed as a temporizing measure while other steps are taken. It loses its initial effect after the first day or two of continuous use. The physiologic effects of inhaled prostacyclin on oxygenation and pulmonary arterial pressure can occasionally be impressive, but its routine clinical benefit has yet to be demonstrated.

**Surfactant**

Because ARDS is characterized in part by microatelectasis, inflammation, and deficiency of viable surfactant, the exogenous replacement of this important biologic substance has a clear rationale. Beyond doubt, surfactant replacement has had a beneficial impact on the care of premature infants in respiratory distress. To date, however, results of multiple clinical studies of surfactant replacement in adults have been profoundly disappointing. Whether inefficacy relates to the method of delivery, type of formulation, inherent nature of the disease, imprecisely defined study populations, or timing of administration is unclear. Without substantiation of its benefit, surfactant cannot be recommended for this clinical application in adults.

**A Lung-Protective Approach to Ventilating ALI and ARDS**

Although definitive clinical data are needed to confirm the wisdom of adopting a pressure-targeted approach, a rational strategy for ventilating patients with ALI can be formulated based on firm theoretical and experimental grounds (Table 24-12 and Fig. 24-17). Such a strategy recognizes that several mechanically distinct alveolar populations coexist within the acutely injured lung, that a poorly chosen ventilatory pattern can be damaging, and that the underlying pathophysiology changes over time. This approach gives higher priority to controlling maximal, minimal, and driving transalveolar pressures than to achieving normocapnia.

Assuming that oxygen and ventilatory demands have been minimized, that FiO$_2$ is kept ≤0.7, and that fluid balance and cardiac function have been optimized, the essential strategic elements are as follows:

1. Sufficient end-expiratory transalveolar pressure must be used to avert tissue damage resulting from surfactant depletion or tidal stresses associated with repeated opening and closure of collapsible units during the breathing cycle. Although improved arterial oxygenation tends to parallel effective recruitment, CO$_2$ retention is a consequence of alveolar overdistension.

2. Because alveolar subpopulations with nearly normal elastic properties may coexist alongside flooded or infiltrated ones, the clinician must avoid applying tidal transalveolar pressures greater than the normal lung
tissue is designed to sustain. When breathing is passive, this pressure generally corresponds to end-inspiratory static airway pressures (“plateau” pressures) less than 30 cm H$_2$O and driving pressures less than 16 cm H$_2$O, but higher values may sometimes be permissible, depending on the stiffness of the chest wall. Conversely, limiting static airway pressure to 30 cm H$_2$O (or any other target) does not guarantee safe ventilation when the patient actively triggers breathing and exerts an unknown end-inspiratory pressure on the pleural side of the lung. Any exertion must be limited, and neuromuscular blockade is a valuable adjust especially when used for less than 48 hours early in the course. Empirically select an appropriate combination of PEEP and tidal volume, using the principles of initial recruitment, decremental setting of PEEP, and respecting the damaging potential of excessive plateau pressure. (See “Selecting PEEP and Tidal Volume in ARDS,” Chapter 9.)

<table>
<thead>
<tr>
<th>Table 24-12. A General Lung-Protective Strategy for Ventilating ARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tailor ventilatory strategy to the phase of the disease (higher titrated PEEP in early stage; withdraw PEEP later)</td>
</tr>
<tr>
<td>Minimize oxygen demands</td>
</tr>
<tr>
<td>Hold FiO$_2$ &lt; 0.70 whenever safely possible</td>
</tr>
<tr>
<td>Consider limited duration of neuromuscular blockade</td>
</tr>
<tr>
<td>Consider early prone positioning</td>
</tr>
<tr>
<td>Minimize pulmonary vascular pressures</td>
</tr>
<tr>
<td>Control plateau and driving alveolar pressure, not PaCO$_2$</td>
</tr>
<tr>
<td>Maintain recruitment of unstable alveoli in the early phase by proning, recruitment maneuvers, and decremental PEEP</td>
</tr>
<tr>
<td>Maintain sufficient total end-expiratory $P_{alv}$</td>
</tr>
<tr>
<td>Avoid large $V_T$ and use least mean $P_{alv}$ required to meet unequivocal therapeutic goals</td>
</tr>
<tr>
<td>Use PEEP judiciously, set in titrated fashion to selected physiologic endpoint</td>
</tr>
<tr>
<td>Hold transalveolar plateau pressure &lt;20 cm H$_2$O</td>
</tr>
<tr>
<td>Hold airway plateau and driving pressures ≤25 and 15 cm H$_2$O, respectively</td>
</tr>
<tr>
<td>Consider making necessary increases in mean $P_{aw}$ by changing the inspiratory time fraction</td>
</tr>
<tr>
<td>Consider specialized adjunctive measures to improve gas exchange and O$_2$ delivery</td>
</tr>
<tr>
<td>Inhaled vasodilators (nitric oxide or prostacyclin)</td>
</tr>
</tbody>
</table>
3. When not contraindicated, hypercapnia should be accepted from the onset of therapy in preference to violating the guidelines of controlling alveolar pressure. Deep sedation and/or paralysis may be required. Permissive hypercapnia may be difficult to implement in the presence of metabolic acidosis, when other measures (e.g., dialysis or ECCO$_2$R) may be needed adjunctively.


1. The prone position should be considered for patients with severe disease who are difficult to oxygenate. Prone positioning generally offers its greatest oxygenation benefit relatively early in the course of illness.

**SUGGESTED READINGS**


• Key Points

1. Three major mechanisms cause or contribute to ventilatory failure: deficient central drive, ineffective muscular contraction, and excessive breathing workload. Important factors contributing to the minute ventilation requirement include levels of alertness, agitation, pain, body temperature, metabolic stress, ventilatory dead space fraction, nutritional status, and high breathing effort.

2. Although isolated disorders of central ventilatory drive are uncommon as sole causes of respiratory failure, they frequently serve as background conditions that lead to acute decompensation when the breathing workload increases or muscular capability is impaired. Sedatives, sedating antidepressants, psychotropic agents, hypnotics, and opiates must be used very cautiously in elderly patients, patients with chronic sleep deprivation, and patients with subacute or chronic CO₂ retention.

3. An investigation of the cause for ventilatory failure should include systematic evaluation of ventilatory drive, minute ventilation, the pressure required per liter of ventilation, and neuromuscular performance. The electrolyte, chemistry, and medication profile must be carefully reviewed. Therapy to reverse ventilatory failure should be guided by knowledge of the underlying physiologic disturbance.

4. Signs and symptoms suggestive of upper airway obstruction include the following: inspiratory limitation of airflow, stridor, difficulty clearing airway secretions, altered voice or cough, marked accentuation of dyspnea by exertion or hyperventilation, and altered breathing symptoms with position changes or neck movements.

5. The nonintubated patient with upper airway obstruction may benefit from maintaining the head-up position, breathing helium-oxygen mixtures, and receiving continuous positive airway pressure (CPAP). Glottic edema that occurs postextubation may also respond to racemic epinephrine aerosols, upright positioning, and corticosteroids. Other key measures include decreasing pleural pressure swings by reducing minute ventilation requirements, relieving bronchospasm, providing high-flow nasal oxygen, and eliminating retained airway secretions and excess edema.

6. Specific danger signs in asthma that warn of the need for urgent intubation include deteriorating mental status, a wide paradoxical pulse, severe hyperinflation, inability to talk in complete sentences, CO₂ retention, acidosis, and cyanosis.

7. Occlusive secretion plugging of the airways may be widespread in status asthmaticus. Appropriate therapeutic interventions include β-adrenergic and anticholinergic aerosols, corticosteroids, and mechanical ventilation. Magnesium sulfate, mucolytics, and mucus lubricants are often helpful.

8. Many patients with chronic obstructive pulmonary disease also have underlying ischemic heart disease that complicates their management. Atrial arrhythmias are unusually common and problematic for these patients. Positive end-expiratory pressure or CPAP often helps to offset autotranspired end-expiratory pressure and improve triggering sensitivity, thereby decreasing the work of breathing in flow-limited patients. Bronchial hygiene assumes a crucial role in management.

9. Noninvasive ventilation has an established place in managing acute exacerbations of chronic obstructive pulmonary disease. Response is most likely when the patient is alert, tolerant of the mask interface, and supported early in the hospital course. When intubation is required, care should be taken to avoid overventilating the patient and to maintain adequate nutrition.
10. Sleep-disordered breathing, derangements of thoracic configuration (obesity, pleural effusion or pneumothorax, kyphoscoliosis), excess total body water, electrolyte disturbances, and diaphragmatic dysfunction often contribute to ventilatory failure.

**PATHOGENESIS OF VENTILATORY FAILURE**

**Definition**
Ventilatory failure is the inability to sustain a sufficient rate of CO$_2$ elimination to maintain a stable pH without mechanical assistance, muscle fatigue, or intolerable dyspnea. Failure to maintain adequate alveolar ventilation usually is recognized by CO$_2$ retention and acidosis. Although a rise in PaCO$_2$ to a level higher than 50 mm Hg has been suggested as definitive, ventilatory failure can occur even when PaCO$_2$ falls to a value lower than its chronic level (which itself may exceed 50 mm Hg). For example, a modest metabolic acidosis may exhaust the limited ventilatory reserve of a patient with quadriplegia, severe airflow obstruction, or acute respiratory distress syndrome (ARDS). In similar fashion, hypocapnic alkalosis may deteriotate to “normal” values for pH and PaCO$_2$ as ventilatory failure develops in a fatiguing asthmatic patient. Conversely, many patients comfortably maintain PaCO$_2$ levels higher than 50 mm Hg on a chronic basis, without satisfying the aforementioned definitions.

**Mechanisms of Ventilatory Failure**
To maintain effective ventilation, an appropriate signal must first be sent from the brain to the ventilatory muscles. The muscles must then contract with enough force and coordination to generate the fluctuating pleural pressures that drive airflow. The ventilatory power required depends on the difficulty of gas movement and the minute ventilation requirement. Three major mechanisms cause or contribute to ventilatory failure: deficient central drive, ineffective muscular contraction, and excessive workload (Table 25-1). The primary physical signs of ventilatory overstress or fatigue are vigorous use of accessory ventilatory muscles, tachypnea, tachycardia, diaphoresis, and paradoxical motion of the chest or abdomen. In coma, the breathing pattern of ventilation failure may be slowed, eventually becoming irregular and gasping in the agonal phase.

**General Principles of Managing Ventilatory Failure**
Ventilatory failure is managed by defining its cause, by correcting reversible problems, and by providing mechanical support when required. If the cause of ventilatory failure is not obvious, bedside measurements intended to determine the mechanisms at work are especially important. Ventilatory workload is reflected in the minute ventilation ([$V$ with dot above]$_E$) and machine pressures needed to deliver the tidal volume (see Chapter 5). Important factors contributing to the [$V$ with dot above]$_E$ requirement include levels of alertness, agitation, pain or discomfort, body size and temperature, pathologic metabolic stress (sepsis, trauma, burns, etc.), ventilatory dead space, fraction, nutritional status, and the work of breathing. The difficulty of chest inflation per liter of ventilation is best gauged by the peak dynamic and static (plateau) inflation pressures as well as by the estimated values for resistance, compliance, and auto-PEEP. Neuromuscular function is evaluated by observing the ventilatory pattern, the tidal volume and breathing frequency, and the actions of the respiratory muscles. At the bedside, the appropriateness of ventilatory drive is often best assessed by examining the pH and PaCO$_2$ in relation to
breathing effort. (e.g., if PaCO$_2$ is high and pH is low, drive may be inadequate, muscular responsiveness may be inappropriate, or both; evidence of patient agitation, dyspnea, or distress argues for primacy of the latter.) Integrative indices of demand and capacity, such as the rapid shallow breathing index or the tidal mouth occlusion pressure ($P_{0.1}$), which is used clinically as a quantitative drive index, may be helpful when assessing the continuing need for machine support (see Chapter 10).

<table>
<thead>
<tr>
<th>Table 25-1. Causes of Ventilatory Failure</th>
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</thead>
<tbody>
<tr>
<td><strong>AIRFLOW OBSTRUCTION</strong></td>
</tr>
<tr>
<td>Upper airway obstruction</td>
</tr>
<tr>
<td>Extrathoracic</td>
</tr>
<tr>
<td>Intrathoracic</td>
</tr>
<tr>
<td>Functional (OSA)</td>
</tr>
<tr>
<td>Lower airway obstruction</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>Bronchial stenosis (transplant, trauma, tumor)</td>
</tr>
<tr>
<td><strong>INTRINSIC MUSCULAR WEAKNESS</strong></td>
</tr>
<tr>
<td>Skeletal muscles</td>
</tr>
<tr>
<td>Weakness</td>
</tr>
<tr>
<td>Neuromuscular impairment</td>
</tr>
<tr>
<td>Quadriplegia</td>
</tr>
<tr>
<td>Myopathy</td>
</tr>
<tr>
<td>Drugs, electrolytes</td>
</tr>
<tr>
<td>Diaphragm paralysis or dysfunction</td>
</tr>
<tr>
<td><strong>INEFFECTIVE MUSCULATURE</strong></td>
</tr>
<tr>
<td>Thoracic configuration</td>
</tr>
<tr>
<td>Chronic</td>
</tr>
<tr>
<td>Kyphoscoliosis</td>
</tr>
<tr>
<td>Thoracoplasty</td>
</tr>
<tr>
<td>Acute</td>
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</tbody>
</table>
Correcting Reversible Factors

The quest to determine the cause for ventilatory failure should be guided by a systematic evaluation of ventilatory drive, \([V\text{ with dot above}]_E\), the work of breathing, and neuromuscular performance. In passively ventilated patients, resistance and compliance can be measured during constant flow ventilation (see Chapter 5). Rational therapy to reverse ventilatory failure depends upon the underlying defect and its severity (Table 25-2). Impedance can be improved by relieving airway obstruction (bronchodilation, secretion clearance, placement of a larger endotracheal tube, etc.), by increasing parenchymal compliance (reduction of atelectasis, edema, and inflammation), and by improving chest wall distensibility (drainage of air or fluid from the pleural space, relief of abdominal distension, upright body positioning, muscle relaxation, or analgesia). A common problem overlooked in ventilated patients is a closed circuit suction catheter inadvertently left in an advanced position beyond the Y-piece. This partial occlusion dramatically narrows the effective caliber of the endotracheal tube and is easily remedied by withdrawing the catheter to its usual position.

Serum chemistries and the medication list must be carefully reviewed for potential suppressants of mental status or muscular strength. Neuromuscular efficiency should be optimized by ensuring alertness, maintaining the patient in an appropriate position (usually as upright as possible), relieving pain, and addressing electrolyte disturbances, nutritional deficiencies, and endocrine disorders. Elevations of ammonia, an endogenous suppressor of consciousness and drive to breathe, should be addressed by reducing correctable sources of its generation—for example, upper GI bleeding, valproic acid, etc.—by encouraging its gut elimination (lactulose). Although Addison disease is rare, adrenal insufficiency (absolute or, more commonly, relative) is surprisingly common among critically ill and chronically debilitated patients who undergo major physiologic stress. Measures that improve cardiac output or arterial oxygenation also will improve neuromuscular performance. Treatable neuromuscular disorders (e.g.,...
myasthenia, polymyositis, Parkinson disease) should not be overlooked. Some problems of decreased ventilatory drive are self-limited (e.g., sedative or opiate excess); others improve with nutritional repletion, electrolyte adjustment (metabolic alkalosis), hormone replacement (e.g., hypothyroidism), or recovery of mental status. Very few respond to nonspecific ventilatory stimulants such as progesterone. Unfortunately, many such problems are refractory to drug manipulation and must be treated by optimizing ventilatory mechanics with the goal of reducing the work of breathing sufficiently to restore compensation.

### Table 25-2. Reversible Factors in Ventilatory Failure

<table>
<thead>
<tr>
<th>EXCESSIVE VENTILATION REQUIREMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Increased CO₂ generation</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Agitation</td>
</tr>
<tr>
<td>Work of breathing</td>
</tr>
<tr>
<td>Excessive calories</td>
</tr>
<tr>
<td>Increased dead space</td>
</tr>
<tr>
<td>Airway apparatus</td>
</tr>
<tr>
<td>Hypovolemia</td>
</tr>
<tr>
<td>Vascular obstruction</td>
</tr>
<tr>
<td>ARDS</td>
</tr>
<tr>
<td>Congestive heart failure</td>
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</table>

<table>
<thead>
<tr>
<th>INCREASED IMPEDANCE TO VENTILATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretions</td>
</tr>
<tr>
<td>Bronchospasm</td>
</tr>
<tr>
<td>Airway apparatus</td>
</tr>
<tr>
<td>Pleural air or fluid</td>
</tr>
<tr>
<td>Abdominal distension</td>
</tr>
<tr>
<td>Auto-PEEP</td>
</tr>
<tr>
<td>Pulmonary edema</td>
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</tbody>
</table>

<table>
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<tr>
<th>IMPAIRED MUSCLE STRENGTH AND ENDURANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional deficiency</td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
</tr>
</tbody>
</table>

\[ \text{PO}_{4}^{2-}, \text{Mg}^{2+}, \text{K}^{+} \] 
| Endocrine disorders |
Mechanical Support

The general principles of intubation, mechanical ventilation with positive pressure, and weaning are presented elsewhere (see Chapters 6, 7, 8, and 10). Noninvasive ventilation (NIV) offers an attractive option for many patients with mild-to-moderate disease with rapidly reversible etiologies for ventilatory failure. Modern interfaces that minimize CO₂ rebreathing (apparatus dead space) while prioritizing comfort have greatly enhanced their effectiveness. Providing conditioned gas by high-flow nasal cannula (HFNC) offers modest ventilatory assistance and is a good option for well-selected and very mildly affected patients.

SPECIFIC PROBLEMS CAUSING VENTILATORY FAILURE

Airflow Obstruction

Airflow may be obstructed at any level of the tracheobronchial tree. Even in the absence of underlying lung pathology, discrete lesions cause symptomatic airflow obstruction if located at the level of the larynx, trachea, or central bronchi (upper airway obstruction [UAO]). Mediastinal compression because of fibrosis, granuloma, or neoplasia can narrow the trachea or major bronchi. Obstruction may be exacerbated by supine positioning in obese patients and those with severe COPD. Diffuse diseases of the airways (asthma, chronic bronchitis, emphysema, bronchiectasis, cystic fibrosis, etc.) usually limit the flow in peripheral air channels (<2 mm in diameter). For certain patients with asthma, however, the primary problem may center on the larynx and upper airway. Aspiration, reflux esophagitis, morbid obesity, retained airway secretions, and congestive heart failure (CHF) routinely contribute to airflow obstruction.

Upper Airway Obstruction

Sedentary patients with low ventilation requirements and UAO may remain relatively symptomfree until the airway lumen achieves a surprisingly small diameter. Dyspnea then progresses disproportionately to any further decrements in caliber or activity. The complaints of UAO may be difficult to distinguish from those of lower airway disease and may include cardiovascular as well as pulmonary symptoms.

Signs and Symptoms of UAO

The following signs and symptoms are particularly suggestive of UAO (Table 25-3).

1. **Inspiratory limitation of airflow.**
2. **Stridor.** This shrill, inspiratory sound is particularly common with extrathoracic obstruction. In an adult, stridor
at rest usually indicates a very narrow aperture (diameter <5 mm).

3. **Difficulty clearing the central airway of secretions.**

4. **Cough of a “brassy” or “bovine” character suggests vocal cord dysfunction.**

5. **Altered voice.** Hoarseness may be the only sign of laryngeal tumor or unilateral vocal cord paralysis. (Although not itself responsible, unilateral cord paralysis frequently is associated with processes that do cause obstruction.) Cords paralyzed bilaterally usually meet near the midline, so the voice may be “breathy” or soft but remains audible, despite serious obstruction. Bilateral vocal cord paralysis impairs the ability to generate sound, so the patient must drastically increase airflow for each spoken word. Only short phrases can be spoken before the next breath, and the patient may experience dyspnea when conversing.

<table>
<thead>
<tr>
<th>Table 25-3. Signs and Symptoms of Upper Airway Obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspiratory limitation of airflow (stridor)</td>
</tr>
<tr>
<td>Impaired secretion clearance</td>
</tr>
<tr>
<td>Brassy or bovine cough</td>
</tr>
<tr>
<td>Breathy voice</td>
</tr>
<tr>
<td>Disproportionate exercise intolerance</td>
</tr>
<tr>
<td>Symptom variation with neck movement</td>
</tr>
<tr>
<td>Failure to respond to bronchodilators</td>
</tr>
<tr>
<td>Rapid reversal of dyspnea upon intubation</td>
</tr>
<tr>
<td>Fulminant episodic pulmonary edema</td>
</tr>
<tr>
<td>Frequent panic attacks</td>
</tr>
</tbody>
</table>

*aIncidence of these signs will vary with nature, location, and severity of the obstruction.

6. **Marked accentuation of dyspnea and signs of effort by exertion or hyperventilation.** The explanation of this nonspecific phenomenon is mechanical. During vigorous inspiratory efforts, negative intratracheal pressures and turbulent inspiratory airflow tend to narrow a variable extrathoracic aperture. Exertion is unusually stressful partially because of impeded expiration but primarily because obstruction worsens rather than improves during inspiration, as it does in asthma or chronic obstructive pulmonary disease (COPD).

7. **Change in breathing symptoms with position changes or neck movement.**

8. **Failure to respond to conventional bronchodilator therapy and/or steroids.**

9. **Unexpected ventilatory failure on extubation or precipitous reversal of ventilatory failure by tracheal intubation alone, without ventilatory support.**

10. **Sudden and pulmonary edema unexplained by cardiac failure.**

During asphyxia and severe choking episodes, very forceful inspiratory efforts markedly lower the intrathoracic pressure, increase the cardiac output, and stimulate the release of catecholamines and other stress hormones. The increased loading conditions of the heart, in conjunction with augmented transcapillary filtration pressures, encourage the formation of pulmonary edema.
Diagnostic Tests

The diagnostic workup of UAO may include routine films, computed tomography (CT) or magnetic resonance imaging (MRI) scans of the neck and trachea, and direct visualization by bronchoscopy or laryngoscopy (mirror, direct, or fiberoptic). Multidimensional, reconstructed 3D CT images are usually highly informative. Though ventilation and perfusion scans are rarely used in this context, main bronchial obstruction caused by foreign body, tumor, or mediastinal fibrosis may give rise to strikingly asymmetry. Clues may be also be provided by comparing full inspiratory with full expiratory chest radiographs. In stable, cooperative patients, useful pulmonary function tests may include inspiratory/expiratory flow-volume loops, maximal voluntary ventilation, and diffusing capacity as well as routine unforced and forced expiratory spirometry (Table 25-4). Typically, variable UAO impairs inspiratory flow more than expiratory flow, impairs peak flow and airway resistance disproportionately to FEV₁, and responds extraordinarily well to a low-density gas (helium-oxygen) but not well to bronchodilators (unless there is simultaneous bronchospasm). In cooperative patients, maximum voluntary ventilation characteristically is much less than the value predicted from the FEV₁, whereas vital capacity may be comparatively normal in relation to FEV₁.

Diffuse airway diseases such as asthma and COPD tend to produce a different pulmonary function test profile. However, asthma can have a significant upper airway component, and occasionally, stridor will be a prominent presenting sign. Often, these patients benefit from anxiolytics or psychotropic drugs as well as bronchodilators and steroids. Unlike the diffuse obstructive diseases, which alter lung volume, distribution of airflow, and diffusing capacity, UAO tends to leave the parenchyma unaffected. Diffusing capacity is relatively well preserved.

The flow-volume loop contour depends on (1) the fixed or variable nature of the obstruction and (2) the intrathoracic or extrathoracic location (Fig. 25-1). A fixed lesion inside or outside the thorax blunts the maximal inspiration and maximal expiration to a similar degree, giving a “squared off” loop contour. A variable extrathoracic lesion, surrounded by atmospheric pressure, retracts inward when subjected to negative inspiratory airway pressure but dilates when exposed to positive airway pressure. Conversely, a variable intrathoracic lesion, surrounded by a pleural pressure more negative than airway pressure, dilates on inhalation. On exhalation, the lesion is pushed inward to critically narrow the airway. Unilateral obstruction of a main bronchus may not generate such characteristic curves.

Table 25-4. Pulmonary Function Tests Suggesting Upper Airway Obstruction

<table>
<thead>
<tr>
<th>Test Description</th>
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<tbody>
<tr>
<td>Disproportionately reduced peak flow</td>
</tr>
<tr>
<td>Maximal midinspiratory flow &lt; maximal midexpiratory flow</td>
</tr>
<tr>
<td>Vital capacity well preserved despite severely reduced FEV₁</td>
</tr>
<tr>
<td>MVV&lt;sup&gt;a&lt;/sup&gt; &lt; 30 × FEV₁</td>
</tr>
<tr>
<td>End-expiratory flows relatively well preserved</td>
</tr>
<tr>
<td>Gas exchanging efficiency&lt;sup&gt;b&lt;/sup&gt; relatively well preserved</td>
</tr>
</tbody>
</table>

<sup>a</sup> Maximum voluntary ventilation (L/min).

<sup>b</sup> DLCO referenced to single-breath lung volume (FRC).
Maximal rate of inspiratory airflow is disproportionately curtailed as negative tracheal pressure accentuates resistance through a variable extrathoracic lesion. In similar fashion, the positive pleural pressures generated during forced exhalation selectively limit the airflow across a variable intrathoracic lesion. A fixed lesion at either site limits the maximum flows in both phases.

Management of UAO

The basic principles of managing exacerbated UAO can be summarized as follows: patients with symptoms at rest should be kept under continual surveillance and well monitored until the acute crisis resolves. Although pulse oximetry may give a false sense of security, as O₂ saturation may remain within broad normal limits until the brink of total airway obstruction, physical exhaustion, or full respiratory arrest is reached. Postextubation glottic edema and laryngeal swelling resulting from injury usually peak within 12 to 24 hours and then recede over the following 48 to 96 hours. Racemic epinephrine aerosols may help reduce glottic resistance as they cause topical vasoconstriction and bronchodilate the lower airway to reduce the amplitude of breathing efforts. For spontaneously breathing patients not already receiving ventilatory support, continuous positive airway pressure (CPAP) or BiPAP delivered by mask is often helpful. Upright positioning is favored.

For unusually labile or otherwise precarious patients, intubation and tracheostomy kits, as well as a 14-gauge needle (for cricothyroid puncture), should be at the bedside for emergent use. In an emergency, oxygen can be insufflated via the needle until an airway is secured (see Chapter 6). Relief of bronchospasm is particularly important in the setting of a UAO. Relief of lower (small) airway obstruction reduces the intrapleural pressure swings and the severity of variable upper airway (particularly extrathoracic) obstruction. If there is inflammatory obstruction, tactile stimulation of the involved region must be avoided, and steroids may be helpful. Heliox may also be a reasonable temporizing option, especially for those who cannot tolerate or do not respond well to pressurized masks and whose oxygen exchange is well preserved. The patient should be kept calm but normally alert. Endotracheal intubation or tracheostomy may be needed if ventilatory failure ensues or secretions cannot be cleared. These procedures should be attempted only by experienced personnel. For otherwise stable patients in whom the airway is “high risk” or known to be difficult to intubate, consideration should be given to conducting intubation and/or extubation in an operating environment where the full range of instruments and supportive
Care of the Fresh Tracheostomy (See Also Chapter 6)

Inadvertent decannulation of a recent tracheostomy in a patient with UAO may present a genuine emergency. As a prophylactic measure, many surgeons provide exteriorized stay sutures to help locate and elevate the stoma. Others immobilize the tube by loosely suturing it in place. If decannulation occurs, the first priority should be to maintain oxygenation as attempts are made to reestablish the airway. Oxygen should be provided by face mask or over the open stoma until the airway can be resecured. At least one brief and gentle attempt to reinsert the original tube usually is warranted, but this occasionally proves difficult. A tracheostomy tube of one size smaller should be kept at the bedside, as well as endotracheal tubes of one and two smaller sizes to serve as a temporary airway until the definitive tracheostomy can be reestablished by the experienced personnel.

Whichever airway is selected, proper location must be ensured quickly by the unopposed passage of a suction catheter and effortless manual insufflation and recovery of the tidal volume. If the trachea cannot be entered within the first few minutes, consideration must be given to immediate oral intubation, unless this is contraindicated by spinal injury, aberrant cervical anatomy, or pharyngeal pathology.

![Obstructive Sleep Apnea](image)

**FIGURE 25-2.** Characteristic pulse oximetry tracings for patients with recurrent functional occlusion of the upper airway during sleep. When the upper airway obstructs repeatedly, the patient may spend a significant proportion of total sleep time under hypoxemic conditions.

Obstructive Sleep Apnea

Although usually considered an “outpatient” problem, obstructive sleep apnea (OSA) or central apnea is observed quite often in the intensive care unit (ICU) environment as an isolated problem, complicating a predisposing disease, or made evident by sedation, analgesia, or postextubation swelling of the laryngopharynx.
The prototypical patient with OSA is an obese, middle-aged, male, or postmenopausal female who is predisposed by pharyngocervical anatomy—but numerous exceptions to these stereotypes are encountered, especially under the provocation of physiologic stress, sedation, and fatigue. The wellmonitored patient on low FiO$_2$ will demonstrate typical oscillations of the continuous oximeter and pulse tracings during sleep (Fig. 25-2), and the heroic snoring efforts are hard to miss in this closely observed setting. Most (but not all) patients will demonstrate evidence of CO$_2$ retention during wakefulness as well—a consequence of impaired drive to breathe coincident with or resulting from loaded breathing in a predisposed subject. A tentative diagnosis is made by extended sleep oximetry (with or without electrocardiogram [ECG] and blood pressure recording). As in the outpatient setting, nocturnal noninvasive ventilatory support (e.g., with CPAP or BiPAP, if necessary) is extremely helpful for nonintubated patients who tolerate this intervention.

**Obesity-Hypoventilation Syndrome**

The prevalence of morbid obesity has never been higher in the industrialized “first” world. As a consequence, a once unusual problem, obesity-hypoventilation syndrome (OHS) has become increasingly common. OHS is characterized by extreme obesity and alveolar hypoventilation, hypersomnolence, and hypoxemia, with resulting cyanosis, polycythemia, and plethora. OSA is a frequent (but certainly not ubiquitous) accompanying feature. Increased body weight lowers lung compliance and raises the total mechanical work of breathing. If body weight doubles, for example, the mechanical work performed to expand the lungs and chest wall increases by more than two thirds. This increase has been attributed to closure of small airways and to engorgement of pulmonary capillaries with the increased pulmonary blood volume that occurs in massive obesity. Although it is understood that increased breathing workload is an inherent feature of obesity, most morbidly obese patients do not become hypercapnic and, in those who do, there is little correlation between the degree of obesity and the ventilatory abnormalities. Some endogenous impairment of ventilatory drive of uncertain cause, therefore, appears to be unmasked by the obesity or by the OSA that accompanies it. Depressed ventilatory drive—an abnormality of respiratory control that is genetically inherent or acquired—is suggested by demonstrating that patients with OHS have decreased respiratory responsiveness to both hypoxemia and hypercapnia. Once hypercapnia is underway, renal compensation for hypercapnia raises the plasma bicarbonate concentration, thereby minimizing the usual fall in arterial pH. Attenuation of hypoventilation and hypercapnia during sleep via nasal BiPAP ventilation usually returns PaCO$_2$ to more normal levels during wakefulness.

**Asthma**

Asthma is characterized by airway inflammation, edema, and bronchospasm. The episodic airflow obstruction that results from these processes reverses partially or completely with medication. The trigger for inflammation and bronchospasm may be (1) an inhaled or ingested allergen; (2) a bronchial irritant causing reflex bronchoconstriction (infection, endotracheal tube stimulation, smoke, fumes and odors, aspirated food, oral secretions, or excessively dry, humid, or cold air); (3) emotion; (4) exercise; (5) sinus drainage; (6) gastroesophageal reflux; or (7) pulmonary venous congestion or cardiac dysfunction. Obese patients often have a disproportionately reduced resting lung volume and correspondingly increased airway resistance. For such patients, relative small changes in airway caliber may cause wheezing and hypoxemia that may simulate asthma even if their airways are not hyperreactive. Asthma may cause airway obstruction that never remits completely, but unlike emphysema, it does not routinely disrupt the lung parenchyma.

**Tracheobronchitis**

Although rare, it should be kept in mind that laryngotracheobronchitis can masquerade as refractory asthma. Respiratory syncytial virus, influenza, and pertussis may be the most common infective agents causing
bronchiolitis and wheezing, and appropriate antiviral agents may speed recovery. Herpes tracheobronchitis is more rare, but occurs in intubated elderly patients with extensive burns or immunocompromise. Infiltrates and fever are uncommon. Oropharyngeal signs of herpes often are absent or obscured. The diagnosis is supported by recovery of virus or viral antigen from sputum but must be confirmed by direct inspection. The problem may prove refractory to corticosteroids and bronchodilators until treated definitively with intravenous acyclovir. Occult microaspiration of food or refluxed gastric contents may also cause tracheobronchitis and simulate an asthmatic presentation.

**Physical Diagnosis of Asthma**

When admitted to the ICU, most patients with exacerbated asthma relate a history of gradually worsening dyspnea. These patients usually require intensive therapy extending over several days before resolution. A subset of asthmatic patients, typically in a young age category, develop life-threatening bronchospasm and ventilatory failure with frightening suddenness—over minutes to hours. In these “sudden asphyxic” asthmatics and for those with other asthma variants, upper airway signs may predominate. Inspissated mucus and edema are less prevalent, whereas emotion, an identifiable provocative agent, and asthmatic stridor often figure prominently in the presentation. Life-threatening airflow obstruction often quickly reverses once intubation, sedation, and appropriate pharmacologic therapy are initiated.

Noncritically ill patients with asthma may report few symptoms despite impressively abnormal examination findings and pulmonary function tests. Rhinitis, sinus congestion, postnasal drainage, and cough often coexist. Dyspnea characteristically begins or worsens at night or in the early morning. Hoarseness or gastroesophageal reflux suggests chronic nocturnal aspiration of small volumes of gastric contents. Substernal chest pain developing suddenly in a young patient with asthma suggests associated bronchitis or mediastinal emphysema secondary to alveolar rupture. An asthmatic patient who is unable to converse in complete sentences has severe airflow obstruction and/or fatigue. Because wheezing depends on both degree of obstruction and velocity of airflow, it is detectable with forceful breathing in mild obstruction, reaches loud intensity in moderate obstruction, and disappears in very severe obstruction. Wheezing may be audible only when the patient is supine. Wheezes do not necessarily imply asthma. The differential diagnosis includes left ventricular failure (cardiac asthma), pulmonary embolism, UAO, and bronchitis (acute or chronic).

**Specific Danger Signs**

**DETERIORATING MENTAL STATUS**

Deteriorating mental status often is a harbinger of physical exhaustion and impending ventilatory arrest. Sleep deprivation, muscle fatigue, sustained catecholamine stimulation, and acute cerebral acidosis (occurring just before arrest) are likely contributing factors. When patients with asthma decompensate, they often do so suddenly. NIV is variably effective, and a very low threshold should be maintained for intubating a disoriented, lethargic patient.

**ARTERIAL PULSUS PARADOXUS EXCEEDING 15 TO 20 MM HG**

Normally, as arm cuff pressure is reduced, the discrepancy (the “paradox”) between the point at which the first intermittent systolic Korotkoff sounds are detected and the arterial pressure at which all are heard is less than 8 mm Hg. The respiratory variation of systolic blood pressure increases as airflow obstruction worsens and is made obvious by tracings from patients with indwelling arterial lines. This phenomenon is believed to result from the wide phasic swings of intrapleural pressure necessary for ventilation, which have several effects:
1. Forceful inspiration effectively “afterloads” the left ventricle. Surrounded by very negative pleural pressure, the left ventricle must, nonetheless, raise intracavitary pressure to systemic levels. Systolic pressure falls during inspiration, whereas reduced left ventricular afterload occurs during forced exhalation.

2. Although inflow to the right atrium increases during inspiration, preload to the left ventricle decreases simultaneously because a relatively small quantity of blood returns to the left atrium. Furthermore, the expanded right ventricle impairs left ventricular filling during inspiration because the left and stretched right ventricles share myocardial fibers, the interventricular septum, and the pericardial space.

SEVERE HYPERINFLATION

Hyperinflation increases with the severity of obstruction and with $\dot{V}$. The increase in resting lung volume is produced by the combined effects of air trapping and the need to hold airways open to minimize the work of breathing. Moreover, in very severe attacks of asthma, many air channels are plugged completely and do not communicate with the central airway at all. When such plugging is extensive, severe hyperinflation is evident on the chest radiograph, but auto-PEEP measured in the intubated patient may be misleadingly low, as it reflects only those pressures within alveoli that communicate with the airway at end-expiration (Fig. 25-3). Considerable regional variation of auto-PEEP values is common, whereas the end-inspiratory alveolar pressures may not differ greatly from site to site. In these cases, therefore, the end-inspiratory plateau pressure during flow-controlled volume-cycled ventilation is a much better indicator of gas trapping when tidal volume and PEEP are fixed. Unless otherwise explained, a marked disparity between a high-plateau pressure and a low measurable auto-PEEP (and/or between the appearance of the hyperinflated chest radiograph and auto-PEEP) suggests extensive airway plugging as the basis for gas trapping.
FIGURE 25-3. **Regional variation in auto-PEEP.** The greatest tendency for airway closure and gas trapping tends to occur in dependent regions. Although end-expiratory airway occlusion pressure reflects the average auto-PEEP among open alveolar units, the highest levels of auto-PEEP are encountered by alveoli cut off from the airway opening earlier in deflation.

**CO₂ RETENTION/ACIDOSIS/CYANOSIS**

If the patient remains well compensated, an acute attack of asthma usually elicits mild alveolar hyperventilation and mild-to-moderate hypoxemia. (Typically, pH is greater than 7.40, PaCO₂ is less than 40 mm Hg, and PaO₂ breathing room air generally exceeds 60 mm Hg in a patient without underlying cardiopulmonary disease of another type.) Compensated asthma is unique among the obstructive diseases in promoting alveolar hyperventilation. Significant central cyanosis (implying marked arterial desaturation or *cor pulmonale*), elevated PaCO₂, and acidosis are important danger signs. If the patient does not appear fatigued and retains normal mental status, these findings by themselves do not demand intubation and mechanical support. Once appropriate therapy is under way, however, progressive deterioration in pH, PaCO₂, muscular strength, or
mental status does require mechanical support, almost invariably with intubation.

**Management**

An attack of asthma may be brief, mild, and self-limited or may continue with such protracted severity as to require extraordinary measures. As a rule, the longer the attack persisted before ICU admission, the more slowly it responds to treatment. Asthma must be managed aggressively, with prompt escalation of the therapeutic regimen if the attack does not “break” quickly.

**IN-HOSPITAL TREATMENT**

Lethargy or disorientation, obvious fatigue, and deteriorating arterial blood gases are grounds for immediate admission to the ICU (Table 25-5). Yet, a single arterial specimen showing mild acidosis or PaCO\(_2\) elevation should be interpreted cautiously. Most such patients will require admission to the ICU, but if the patient is alert and both the arterial blood gases and the patient show prompt and marked improvement with initial treatment, ICU admission is sometimes avoidable. Oxygen, corticosteroids, bronchodilators, and intravenous fluids are required for virtually all patients. For specific indications, antibiotics and ventilatory support are needed as well. During an established attack, the patient may not seem to improve for days, only to recover rapidly thereafter without a major change in therapy.

**Oxygen**

Oxygen should be administered by nasal prongs or mask to all patients with less than full arterial saturation of hemoglobin.

**Inhaled Bronchodilators**

Although a focus for management, bronchospasm is by no means the entire (or sometimes even the primary) problem for patients with asthma who require intensive care. Termination of the inflammatory response, resolution of mucosal edema, and clearance of airway secretions are more important, especially in patients who have had respiratory compromise for days before hospitalization. In the setting of status asthmaticus, bronchodilating aerosols do not penetrate deeply into the obstructed airways. (This is especially true for the intubated patient receiving mechanical ventilatory support.) It is generally acknowledged that more frequent dosing of \(\beta_2\)-agonists is required during an acute exacerbation of asthma. In the breathless patient, nebulization is generally superior to metered-dose aerosols. There is no convincing evidence, however, that continuous nebulization is preferable to the same total dose given intermittently. Moreover, intermittent administration encourages the frequent reassessment appropriate to this setting.

<table>
<thead>
<tr>
<th>Table 25-5. Danger Signs in Asthma</th>
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<tr>
<td>Deteriorating mental status</td>
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<td>Arterial pulsus paradoxus &gt;15-20 mm Hg</td>
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<tr>
<td>Progressive hyperinflation</td>
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<tr>
<td>Increasing CO(_2) retention despite Rx</td>
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<tr>
<td>Cyanosis unresponsive to oxygen supplementation</td>
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<tr>
<td>Retained central airway secretions</td>
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<td>Incipient pulmonary edema</td>
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<td>Unstable hemodynamics</td>
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It must be remembered that a rapid and impressive response to bronchodilators is not to be expected in the patient admitted to the ICU with full-blown status asthma who already has been taking such treatment with deteriorating compensation. Furthermore, there are important costs and hazards associated with frequent administration of highdose \( \beta \)-agonists. Very frequent intermittent dosing may interfere with sleep and/or rest of an exhausted patient. Regardless of dosing method, \( \beta \) agents induce agitation, tachycardia, arrhythmia, or hypokalemia. Therefore, a zealous treatment schedule may be counterproductive. These side effects and hazards are even more prevalent when nonaerosolized (enteral or parenteral) \( \beta \) agents are used.

In the hyperacute phase, albuterol can be given every 30 to 120 minutes unless there are limiting side effects. For most patients with asthma, the anticholinergic agents (e.g., ipratropium, atropine) are no more effective than the \( \beta_2 \)-agonists and usually less so. Because ipratropium is absorbed poorly from the airway mucosa, tachycardias, arrhythmias, and hypokalemia are decidedly less common than with the adrenergic agents; therefore, to reduce side effects, many clinicians elect to use them alternately with the \( \beta_2 \) bronchodilators, especially if the patient has a known or suspected cardiac condition. Ipratropium may be less effective in stable asthma but has a good rationale when tachycardia results from the \( \beta_2 \) bronchodilators, when \( \beta_2 \) tachyphylaxis is suspected, or when irritative (vagally mediated) bronchospasm figures prominently in the pathogenesis (e.g., smoke inhalation, chemical exposure, “cardiac” asthma, acute bronchial infection). Anticholinergics should not be administered more often than every 4 to 6 hours, for fear of drying secretions, blurring vision, or causing mental status changes. A combination anticholinergic/\( \beta_2 \)-inhaled bronchodilator may be a good choice for scheduled treatments, supplemented by interspersed doses of pure \( \beta_2 \) agent, as necessary. When severely ill, many nonintubated patients prefer a wet nebulizer to a metered-dose canister, even though some comparative studies fail to show its bronchodilating advantage over a sufficient number of metered puffs. Wet nebulization of more than 10 to 15 mg of albuterol (or its equivalent) may be associated with undesirable cardiovascular stimulation, a fall in serum potassium concentration, or lactic acidosis. Patients predisposed to tachycardia or arrhythmia may benefit from nebulized levalbuterol, a selective \( \beta_2 \)-agonist, which may stimulate the heart less than the mixed isomeric albuterol on which it is based, but this potential advantage may not be clinically apparent. If inhaled bronchodilators are prescribed, careful attention should be directed to the duration of effective action, which varies with dosage. For standard doses:

- Metaproterenol: 2 to 4 hours
- Albuterol: 3 to 6 hours
- Levalbuterol: 4 hours
- Salmeterol: 8 to 12 hours
- Formoterol: 8 to 12 hours
- Ipratropium: 4 to 7 hours
- Tiotropium: 24 hours

Rapidity of the onset tends to be inversely proportional to the duration of action. Inhaled corticosteroids, cromolyn, and nedocromil aerosols, which are intended for prophylactic use, have no place in the management of hospitalized patients. In fact, their irritant effects actually may worsen symptoms during the acute phase.

**Corticosteroids**

Virtually every patient hospitalized for asthma should be given corticosteroids promptly and in high doses. Steroids reduce inflammation, help thin secretions, block components of the allergic response, and may enhance responsiveness to \( \beta \)-adrenergic bronchodilators. Whether superhigh doses of steroids (>125 mg
of methylprednisolone every 6 hours) are preferable to moderately high doses (60 to 100 mg every 6 hours) continues to be debated. The question is not academic; high-dose steroids often interfere with sleep, mood, cooperation, and thinking as well as disturb glucose homeostasis. Although high-dose steroids are generally safe and well tolerated for short periods, profound neuromyopathy, manifest by elevated levels of creatine kinase and protracted weakness, is believed to result from the use of corticosteroids alone or in combination with extended neuromuscular blockade with nondepolarizing agents (see following and Chapter 17). Nevertheless, the danger of uncontrolled asthma clearly outweighs the danger of administering high-dose steroids for a brief period. The therapeutic effects of a single corticosteroid bolus are evident within 4 to 6 hours, peaking within 12 to 16 hours. There remains considerable disagreement regarding optimum delivery methods, doses, and schedules of administration. One rational recommendation is to administer an initial dose of 1 to 3 mg/kg of methylprednisolone (or equivalent) intravenously, followed by a similar dose every 6 to 12 hours until the attack is broken. For many patients, the oral route is equally efficacious and dramatically more cost-effective than parenteral dosing. Once symptoms have improved considerably, the dosage can be cut back to moderately high doses (0.5 to 1.0 mg/kg twice a day) for a few days before tapering gradually to the prehospital dose over 3 weeks. An inhaled steroid can be added at approximately 10 to 14 days, if chronic prophylaxis is indicated. Final tapering to the preattack dose should be performed by the outpatient physician.

Sedation, Paralytics, and Iatrogenic Neuromyopathy

Many patients hospitalized with status asthmaticus are so exhausted that they sleep deeply and require little or no sedation during the first few hours of their intubation. Others, however, will require deep sedation and even muscle relaxants to reduce the ventilatory requirement to tolerable levels and to accept the permissive hypercapnia required to apply safe levels of airway and alveolar pressure (see Chapters 7, 24, and following discussion). Neuromyopathy presents a serious risk in the controlled ventilation of the asthmatic patient. These patients often require controlled ventilation for greater than 48 hours and therefore run serious risk for ventilator-induced diaphragmatic dysfunction (VIDD). Moreover, a significant proportion of such patients will develop generalized neuromyopathy that may impede ventilator disconnection and lead to sustained weakness postextubation. During the period of immobilization, myopathy manifests in the short term as an elevation of muscle enzymes and later as a profound weakness requiring weeks to months for reversal. In the great majority of reported cases of neuromyopathy in asthma, high-dose corticosteroids were given. Most myopathic patients also received nondepolarizing paralytic agents uninterruptedly for longer than 48 to 72 hours, often without the depth of relaxation monitoring. On the basis of current evidence, it seems advisable to limit the use of muscle relaxants to those who clearly need them and to use only the amounts necessary to accomplish partial paralysis for the shortest possible time. This need for paralysis is best established by attempting to withdraw the muscle relaxant entirely several times per day, thereby also allowing the physician to gauge the adequacy of sedation. “Train-of-four” monitoring, titrating to a two-twitch response, is also rational when continuous paralysis is targeted, but the efficacy of twitch monitoring is debated. Furthermore, uninterrupted neural blockade runs the risk of unnecessarily delaying withdrawal of the paralytic agent and may mask underlying alertness.

Theophylline

Although clearly useful for some patients, theophylline derivatives must be used very cautiously (if at all) in status asthmaticus, with appropriate respect for their low therapeutic index. Failure of the left or right ventricle, hepatic disease, life-threatening illness, and certain drugs (notably ciprofloxacin and histamine-blocking drugs) slow its catabolism. Both efficacy and toxicity of theophylline roughly parallel its blood level;
10 to 20 $\mu$g/mL is usually a safe therapeutic range but occasionally may cause arrhythmias. As with most bronchodilators, greater effect can be achieved with higher doses, but response relates only logarithmically to dose, and the incidence of toxic effects accelerates at higher serum levels. Theophylline holds a questionable place in the treatment of the patient with acute asthma who is receiving $\beta$ agonists and corticosteroids simultaneously. Despite its shortcomings, there recently has been a renewed surge of enthusiasm for its carefully monitored use. Some experienced practitioners believe that it improves diaphragmatic function, helps mobilize secretions, and improves cardiac contractility, but these potential benefits are controversial. The weight of current evidence suggests that theophylline seldom adds to the bronchodilating effect of an optimized $\beta$-aerosol regimen, and it has little value as a stimulant to respiratory drive.

The warning signs of theophylline toxicity (nausea, abdominal discomfort, etc.) may not be sensed or reported by seriously ill patients; therefore, frequently obtained serum levels are mandatory. Cardiac arrhythmias predictably develop at levels greater than 25 $\mu$g/mL; in predisposed patients, it is likely that theophylline is arrhythmogenic at much lower levels. Central nervous symptoms (agitation, confusion, seizures, etc.) appear routinely at levels greater than 35 $\mu$g/mL but can be seen in a lower range. Theophylline seizures are problematic because of their resistance to standard anticonvulsants.

**Magnesium Sulfate**

As a smooth muscle relaxant, magnesium sulfate possesses mild bronchodilating effects, believed to relate to modulation of calcium ion fluxes in smooth muscle. Studies conflict, however, regarding its value in refractory asthma. Although the toxicity of a 1- to 2-g dose in patients with normal renal function seems limited to flushing and mild sedation or mild hypotension, most patients simultaneously given full doses of conventional bronchodilators demonstrate little additional benefit.

**Fluids**

After repair of any fluid deficits present on admission, copious fluids are unnecessary and may cause volume overload. Yet, the patient should be kept amply hydrated (2 to 3 L of fluid daily) to aid thinning of secretions. Although physiologic saline may help lubricate viscid secretions and facilitate airway suctioning in intubated patients, hydrating aerosols (mist therapy) may exacerbate obstruction because of bronchospasm or cause swelling in situ of retained secretions. The instillation of saline via the endotracheal tube to aid secretion clearance theoretically may promote pneumonia, but the reality of this reasonable concern has not been convincingly established.

**Respiratory Therapy**

Secretion retention is a very serious problem in asthma and is caused partly by the unusually tenacious nature of the sputum. Many airways are totally plugged, impeding dislodgment of the mucus. Unfortunately, chest percussion and postural drainage are relatively ineffective and poorly tolerated until a measure of bronchospasm has been relieved (usually the second or third day). Until that point, coaching to cough, bronchodilator inhalation, airway humidification, and oxygen therapy approach the limits of useful respiratory therapy services for the nonintubated patient. NIV and CPAP are tolerated poorly by most patients with severe disease but are worth attempting in cooperative patients with more moderate illness (see Chapter 7). Mucolytics (such as hypertonic NaHCO$_3$, acetylcysteine, and dornase) may irritate the twitchy airways of the decompensated asthmatic and must be used concurrently with or immediately after an inhaled bronchodilator. Bronchoscopy and lavage of inspissated mucus may be indicated in weak ventilated patients who fail to improve.

**Mechanical Ventilation**

Mental status or blood gas deterioration that occurs despite aggressive medical therapy is an important
indication for ventilator support. NIV may be helpful in the fully alert, nondeteriorating subject who can tolerate it. Although not as clearly helpful as in exacerbated COPD, NIV may help forestall the onset of fatigue, whereas steroids and bronchodilators make headway against the cause itself. Unlike many patients with COPD, patients with asthma tend to sustain adequate alveolar ventilation during attacks until sudden decompensation occurs. Invasive mechanical support may afford the rest needed for recovery and should not be delayed once a firm indication appears. Although most patients with asthma can be disconnected from the ventilator within 3 to 5 days of intubation, others require considerably longer.

The basic principles of ventilator management during status asthmaticus do not differ greatly from those of other conditions. However, hemodynamic compromise and certain forms of barotrauma (pneumomediastinum, pneumothorax, etc.) are important consequences of gas trapping. Peak alveolar end-inspiratory (plateau) pressure should be monitored closely and kept lower than 30 cm H$_2$O. For most patients, this will mean the acceptance of hypercarbia and respiratory acidosis (permissive hypercapnia). Deep sedation and, in severe cases, muscle relaxants may be required to impose this gentler breathing pattern.

As a guideline, a tidal volume of 6 to 8 mL/kg, a backup frequency of approximately 12 breaths/min, and a flow setting and waveform that provide a 1:2 I:E ratio are a satisfactory starting point for ventilator settings in a patient who is well sedated. Failure to keep end-inspiratory static plateau pressure less than 30 cm H$_2$O should prompt reductions of frequency or tidal volume. Some physicians allow pH to fall to 7.10 (or even lower) if the patient demonstrates good physiologic tolerance, but this approach cannot be advocated for general use. The degree of dynamic hyperinflation is generated by the severity of airflow obstruction, the tidal volume, and the duration of expiration. The duration of expiration is most effectively extended by decreasing the breathing frequency (and minute ventilation). Very rapid inspiratory flow rates are not helpful in reducing gas trapping, raise peak pressures in the central airways, and should be avoided during volume-cycled ventilation. For the same inspiratory time, most severe asthmatic patients will have a lower peak airway pressure with a gently decelerating waveform. Strong, spontaneously triggering patients often prefer “square wave” inspiratory flow or pressure-controlled ventilation to meet their flow demands throughout inspiration.

**Positive End-Expiratory Pressure**

The place of positive end-expiratory pressure (PEEP) in the management of asthma remains controversial. When resistance is volume dependent and flow limited, as it tends to be in this setting, PEEP may possibly improve bronchodilator penetration. In spontaneously breathing patients, CPAP may help even the distribution of ventilation as well as reduce the triggering threshold and the work of breathing (see Chapter 9). However, if expiration is not flow limited, adding PEEP could simply raise both peak and mean alveolar pressures. As a rule, a low level of PEEP (<8 to 10 cm H$_2$O) can be added, as long as end-inspiratory static “plateau” pressure does not rise by the same amount.

### Chronic Obstructive Pulmonary Disease

**Characteristic Features**

The obstructive lung diseases associated with cigarette smoking (primarily emphysema and chronic bronchitis) often coexist but are fundamentally different processes. Emphysema destroys the alveolar surface membrane and blood vessels, reducing elastic recoil and diffusing capacity, leaving the airways collapsible but morphologically intact; emphysematous obstruction of the airway is a functional, not anatomic, problem. Conversely, chronic bronchitis causes airway damage, bronchospasm, and sputum production but leaves the
Parenchyma minimally affected.

Pure cases of emphysema are clinically distinguishable from those of chronic bronchitis. On the chest radiograph, bullae, hyperlucency, diminished peripheral vascular markings, and increased lung volume are often seen in emphysema. CT is vastly superior for detecting these alterations. Such findings differ from the increased bronchovascular markings and more normal lung volumes of chronic bronchitis. Patients with pure emphysema produce little or no sputum. Conversely, chronic bronchitis is defined as an airway disease in which there is habitual sputum production, especially in the morning. (That characteristic is shared by other airway diseases, such as sinusitis and bronchiectasis.)

Emphysematous patients tend to experience breathlessness with minimal exertion but usually do not enter the hospital with exacerbations of their disease until they near their terminal phase. In contrast, patients with chronic bronchitis often seem less distressed by their symptoms but decompensate more frequently.

The vivid caricatures of patients with emphysema as “pink puffers” and patients with chronic bronchitis as “blue bloaters” are overdrawn. Many—if not most—have elements of both. Emphysema tends to destroy capillaries and alveolar septae in proportion to one another, preserving near-normal arterial blood gases at the cost of greater dead space and elevated minute ventilation. Diffusing capacity is impaired. Bronchitis, on the other hand, produces extensive ventilation-perfusion ($V_{\text{dot above}}/Q_{\text{dot above}}$) mismatching and hypoxemia, without impairing the diffusing capacity adjusted for the volume of aerated tissue, and hypercapnia occurs more commonly.

Pulmonary hypertension marks the end stage of both diseases, but for different reasons. In pure emphysema, pulmonary capillaries are destroyed, but normal oxygen saturation of arterial blood is the rule. In chronic bronchitis, pulmonary hypertension develops earlier, as a consequence of persistent alveolar hypoxia. Therefore, cor pulmonale in a patient with bronchitis and hypoxemia may be partially reversed with supplemental oxygen. Cor pulmonale developing in the setting of emphysema is an ominous sign, responding poorly to therapy unless hypoxemia coexists. Despite the aforementioned characteristics, there are many variations of presentation in patients with advanced forms of either chronic obstructive disease.

**Associated Problems**

Hyperinflation helps speed expiratory airflow but increases the elastic work of breathing. Just as importantly, the inspiratory musculature is placed at a serious mechanical disadvantage (Fig. 25-4).
FIGURE 25-4. Respiratory muscle compromise during acute hyperinflation. Normally, the curved hemidiaphragm is positioned optimally to splay the ribs outward during inspiration by its bucket-handle action and by the positive outward abdominal pressure exerted on the ribs in the zone of apposition. The hyperinflated patient may have a flattened diaphragm with no useful inspiratory force vector, lose the zone of apposition, and inspire against the inward recoil of the horizontal ribs. Simultaneously, the work of breathing is increased (see Chapter 10).

Poorly ventilated cystic spaces may fill with fluid when the surrounding parenchyma is infiltrated or flooded (bullitis), a problem simulating cavities or lung abscesses but generally less resistant to therapy. Distinction by chest film or CT usually can be made easily, and the prospect for quick resolution is much better than for abscess.

Pneumonia and CHF often complicate COPD but frequently are difficult to recognize as such because the parenchyma is hyperinflated and distorted.

Heart rhythm disturbances—typically atrial fibrillation, atrial flutter, and multifocal atrial tachycardia—are characteristic of decompensated COPD.

Management
ETIOLOGY OF THE EXACERBATION

The exact cause for many exacerbations of COPD remains unknown. Ischemic heart disease and diastolic dysfunction often coexist. Entry into a rapid atrial rhythm often precipitates dyspnea and altered gas exchange. Cor pulmonale is notoriously difficult to diagnose accurately, especially when a high-quality echocardiogram is not obtainable. Numerous patients with severe disease blame climatic changes (e.g., increased humidity or cold dry air) for their deterioration. Treatable causes (infection, pneumothorax, pleural effusion, congestive failure, embolism, etc.) must be addressed (see Table 25-2).

OXYGEN THERAPY

Although it is true that high inspired fractions of oxygen may blunt ventilatory drive in susceptible individuals, judicious administration of the correct dose of oxygen can be lifesaving. Reversal of hypoxemia may diminish hypoxic drive and work of breathing. In symptomatically hypoxic patients, oxygen improves alertness and muscular function and helps relieve cor pulmonale as well. (For this latter reason, oxygen often proves an effective diuretic.)

Although Venturi masks deliver a fixed FiO$_2$ and should be used when control of the inspired O$_2$ fraction is crucial, nasal prongs are more comfortable for patients with dyspnea and allow expectoration without interrupting the flow of oxygen.

Most patients respond to relief of hypoxemia by retaining slightly more CO$_2$ because hypercapnic drive and hypoxic drives are both reduced by supplemental oxygen. Two rules are useful: first, patients at risk to retain excessive CO$_2$ are those who already manifest some degree of hypercapnia before O$_2$ therapy is initiated. Second, in otherwise stable patients given “low-flow” oxygen, the rise in PaCO$_2$ generally is less than 10 mm Hg and usually occurs within the first hour of oxygen administration. Therefore, rather than withhold oxygen, the appropriate strategy is to raise PaO$_2$ to 55 to 60 mm Hg, watch the patient closely for signs of obtundation, obtain blood gases 20 to 30 minutes after the FiO$_2$ was increased, and adjust the oxygen flow rate accordingly. The therapeutic endpoint is an acceptable PaO$_2$, documented by blood gas analysis.

MEDICATION REGIMEN

Bronchodilator therapy is similar to that already described for asthma. Anticholinergic aerosols, however, may be somewhat more effective in these “irritant” forms of bronchospasm. These include ipratropium (Atrovent) and tiotropium (Spiriva), a long-acting “maintenance” agent that is increasingly used in the hospital setting. For acutely ill patients, the former is often combined with albuterol, an adrenergic agent of similar duration of action. The reversible component of bronchospasm in COPD is usually small, and such patients are generally older and more fragile than those with asthma. Fluid/electrolyte balance, attention to cardiac issues (e.g., diastolic dysfunction), oxygen therapy, and respiratory therapy assume greater importance than in asthmatics. Improving nutrition is helpful over the medium and long term.

Thick green or deep yellow sputum with leukocytes and Gram-stainable intracellular organisms should be treated with an appropriate antibiotic, whereas sputum eosinophilia suggests the probable utility of corticosteroids. (Both medications are given almost routinely, even in the absence of such data.) Although cultures are infrequently performed, the choice of antibiotic ideally should be guided by the sputum smear and by knowledge of the organisms to which these patients are especially vulnerable (i.e., Haemophilus influenzae, Streptococcus pneumoniae, Mycoplasma, and Moraxella catarrhalis) (see Chapter 26). If no organism is seen, a virus or Mycoplasma is the likely infectious cause of the exacerbation. In some regions of the country, Legionella is a prevalent community-acquired pathogen that is difficult to identify on Gram stain but often detected by urinary
antigen testing, as are some strains *Pneumococcus*. Practically speaking, antibiotics are usually begun empirically, with amoxicillin, doxycycline, and azithromycin all frequent and rational choices as they address the most commonly encountered organisms. Selected cephalosporins and fluoroquinolones (e.g., moxifloxacin) are also effective and may offer advantages regarding dosing frequency or convenience, but they are generally more costly. Macrolides (erythromycin-like) drugs have anti-inflammatory as well as antibacterial properties and are frequently part of the selected regimen. Duration of treatment should be limited to 5 to 7 days unless continued fever and/or infiltrates are worrisome for pneumonia.

A patient who fails to respond despite appropriate initial measures probably should receive a trial of corticosteroids. This recommendation includes the majority of those admitted to the hospital who are not critically ill. There has been some concern that steroids are not routinely helpful in critically ill COPD patients and clearly promote hyperglycemia. Nonetheless, because of their relatively low risk to benefit ratio, they are rarely withheld. Although controversy continues regarding proper dosing and duration, it is generally agreed that massive doses of corticosteroids similar to those given in asthma should be avoided. Very high doses of steroids disrupt thinking, interfere with sleep, encourage protein wasting, elevate blood urea nitrogen (BUN) and white blood cell count, predispose to infection, and cause fluid retention. Metabolic alkalosis, hyperglycemia, and gut dysfunction or ulceration also are to be expected. A reasonable schedule is to give 0.25 to 0.5 mg/kg of methylprednisolone or its equivalent every 6 hours during the first 24 to 48 hours of an acute crisis, with conversion to oral prednisone and tapering thereafter to the patient's baseline over a 10- to 14-day period.

**RESPIRATORY THERAPY**

Most problems can be reversed by relieving hypoxemia, treating infection or fluid overload, and improving secretion clearance with the respiratory therapy techniques of coughing, deep breathing, and intensified bronchodilator therapy. Retained airway secretions seriously impair airflow, especially among those with diseased bronchi of the smallest caliber. Effective bronchial hygiene may therefore assume a crucial role in the management of hospitalized patients with COPD. The important roles of hydration, bronchodilation, steroids, and antibiotics have already been discussed. Mucus lubricants, such as guaifenesin, are often helpful as expectorants. Yet, to maintain clear air channels, the patient often must be actively stimulated to cough, using endotracheal suctioning and/or vibropercussion of the chest wall or airway if necessary. A variety of devices are currently available that are intended to mobilize or extract airway secretions. Vest and/or airway vibropercussion appears to have genuine value for this purpose; clinical experience indicates that these techniques are often effective when secretions are plentiful and the treatment is well tolerated. Although promising, adequately rigorous, scientifically collected clinical documentation is still lacking. Cough assist devices slowly inflate and then rapidly assist deflation of the lungs to help expectoration. The concept is attractive and anecdotal reports suggest efficacy, but again the existing literature is mainly descriptive rather than conclusive. It should be remembered in treating all phases and severities of ventilatory failure that body positioning affects airway caliber, tendency for airway closure, and respiratory muscle performance. For exacerbated asthma and COPD, upright postures are important to prioritize, especially when obesity is a component of the challenge.

**MECHANICAL VENTILATION**

**Noninvasive Ventilation**

Whenever safe to avoid, intubation and mechanical ventilation must be avoided for the following reasons:

1. Most patients without advanced *cor pulmonale* tolerate mild-to-moderate hypoxemia and mild acidosis quite well.

2. An effective cough clears the peripheral airways better than endotracheal intubation and suctioning.
3. Patients with COPD are at particular risk for the complications of mechanical ventilation (e.g., infection, hypotension, barotrauma) and can be especially difficult to wean because of the high work/cost of breathing, weakness, and muscular discoordination.

4. When intervention is early enough, many patients with exacerbated COPD may respond well to NIV by facial mask or even less aggressive assistance by high-flow nasal oxygen (see Chapter 7). Even though NIV is of unquestioned benefit for many patients who remain alert and not precipitously deteriorating, some centers lack the highly trained and motivated nursing and respiratory care practitioners required to implement (and discontinue) this technique safely, effectively, and expeditiously. Early intervention, careful coaching of the patient, a comfortable and dead space-clearing mask interface, careful titration of inspiratory and expiratory pressures, and a high degree of vigilance are essential to a successful outcome (see Chapter 7).

As discussed in Chapter 7, NIV holds a central role in the treatment of exacerbated COPD. When compared to invasive ventilation, successful NIV offers several advantages: (1) improved comfort, reducing the need for analgesic and/or sedative drugs; (2) easy application and removal of the interface; and (3) preserved abilities to cough, swallow, and verbally communicate. Furthermore, the risk of ventilator-associated pneumonia and other infectious complications is reduced, which makes NIV particularly appealing for immunosuppressed patients.

Despite these positive characteristics, NIV is contraindicated in those necessitating cardiorespiratory resuscitation or who are continuously agitated and uncooperative. NIV is also inappropriate for patients unable to protect the airway or effectively manage airway secretions, for those requiring high levels of airway pressure, and for those in nonhypercapnic coma.

NIV outcome depends on logistic factors, such as location of treatment, caregiver expertise, and specific technical features related to ventilators and interfaces. These latter are of fundamental importance. Air leaks are ubiquitous and often variable moment to moment. If excessive, leaks can promote NIV failure by contributing to patient-ventilator asynchrony and discomfort. Leaks can be contained by using ventilators equipped with dedicated NIV software capable of detecting and compensating for them. The interface has to fit well to the facial anatomy and be comfortable enough to make protracted NIV well tolerated. As patients with ARF usually breathe with mouth open, full face masks are preferred initially. However, no single interface suits all patients, and the choice must be individualized. When prolonged near-continuous NIV application is necessary, rotating among several types of interface may be advisable.

Early NIV often prevents frank decompensation and is strongly recommended as a first option for many hypercapnic patients with COPD exacerbations and/or cardiogenic pulmonary edema. NIV can facilitate the extubation of COPD patients with lingering but improving hypercapnic respiratory failure; however, as for all instances where NIV is used as an alternative to invasive ventilation, this application requires an ICU team highly experienced with these techniques. It is also essential to select a comfortable and well-fitting mask that minimizes its imposed dead space and CO₂ rebreathing. Recent developments in head-enclosing "helmet" technology, though not yet widely implemented, may further extend the range of effective options. In patients at concerning risk of extubation failure, NIV applied soon after tube extraction helps avert reintubation and improves overall outcomes. Well-humidified HFNCs are an attractive alternative for many in this postextubation patient group and may help reduce reintubation rates in patients at relatively low risk. Failure rates among patients at high risk of reintubation appear similar for HFNC and NIV.

**Indications for Intubation**

Indications for intubation include deteriorating mental status, loss of effective cough (with retained secretions), progressive respiratory acidosis despite
aggressive medical and respiratory therapy, failed NIV or HFNC, and unstable hemodynamics.

If mechanical assistance is necessary, care should be taken not to overventilate with respect to the chronically stable state of CO₂ retention, a development signaled by the sudden development of metabolic alkalosis when mechanical assistance is begun.

Throughout the course of invasive ventilatory support, the staff must check periodically for evidence of dynamic hyperinflation (auto-PEEP) and its response to PEEP. Simultaneous airway pressure and flow tracings help greatly in this assessment (see Chapters 5 and 9). The auto-PEEP effect is associated not only with cardiovascular consequences but also with increased work of breathing and varied forms of patient-ventilator asynchrony. Increased air trapping and expiratory efforts occur during spontaneous breathing as well. Weaning must be undertaken as soon as feasible but should be conducted cautiously to avoid cardiopulmonary decompensation or panic attacks (see Chapter 10).

TREATMENT OF ARRHYTHMIAS AND CARDIAC DYSFUNCTION

Atrial and ventricular arrhythmias of all types occur commonly because of right atrial overdistension, catecholamine release, medication effects, pH and electrolyte disturbances, hyperinflation-related heart-lung interactions, and hypoxemia. The onset of atrial fibrillation can severely impair the efficiency of the ventricular pump and precipitate deterioration. Multifocal atrial tachycardia (chaotic but coordinated atrial contraction originating from at least three pacemaking foci; see Chapter 4) is a characteristic rhythm that often responds only to the relief of metabolic derangement and respiratory failure. In certain cases, a calcium channel blocker (e.g., diltiazem) can effectively slow the rate. Caution is indicated, however, because some antiarrhythmic agents worsen [V with dot above] [Q with dot above] matching, impair the myocardial performance, or impede the conduction (see Chapters 3, 4, and 22). In such patients, ischemic cardiac disease frequently coexists and may present with atypical signs or symptoms. In managing ventilation, the clinician should remain vigilant to the possibility of occult ischemia, CHF, and diastolic dysfunction—as well as cor pulmonale.

NUTRITION

The ability of the patient with COPD to cope with the respiratory workload depends on the strength and endurance of the ventilatory pump. Reversal of chronic malnutrition cannot be accomplished quickly, but maintaining adequate calorie intake is vital. Diaphragmatic bulk parallels body weight. Although it is possible to generate excessive CO₂ by overfeeding, this seldom presents a problem for hospitalized patients who are able to eat normally. Instead, attention should focus on providing adequate nutrition (ideally, a balanced diet providing approx. 2,000 cal daily). Large meals or brisk enteral feedings may cause abdominal distension, discomfort, and breathing difficulty. Relief and prevention of obstipation are particularly important to breathing comfort but are frequently overlooked.

Neuromuscular Dysfunction

As causes of ventilatory failure, extrapulmonary disorders that involve the central drive mechanism, chest wall, or respiratory muscles typically have relatively well-preserved pulmonary gas exchanging function. Hypoxemia usually presents a secondary problem, and minute ventilation requirements are generally modest. In such settings of diminished ventilation reserve, taking special care to avoid the superimposition of a second process (metabolic acidosis, aspiration, etc.) takes on special importance.

Functional Anatomy of the Respiratory Muscles

In healthy individuals, quiet tidal breathing is accomplished by active inhalation and passive deflation. The inspiratory muscles include the diaphragm (responsible for the major portion of ventilation at all but extreme work rates) and the accessory group, primarily the external and parasternal intercostals, scalenes, and strap muscles
of the neck. Normally, expiratory muscle activity is required for expulsive efforts (cough, sneeze, defecation, etc.), for high levels of ventilation (>10 to 15 L/min), and for breathing against a significant resistive load (as during an exacerbation of asthma or COPD). Hyperinflation resulting from PEEP or auto-PEEP may elicit pursed lips breathing with expiratory muscle activation. An increased workload and impaired pump function often coexist in patients presenting with ventilatory failure. Because maintenance of alveolar ventilation requires a pressure gradient sufficient to overcome resistive and elastic forces, any condition that interferes with the ability to generate negative intrathoracic pressure (e.g., weakness, abnormal thoracic configuration, or muscular incoordination) will stress the system and may lead to ventilatory failure, with or without increased force requirements or derangements of gas exchanging efficiency.

**Components of Pump Efficiency**

**MUSCULAR STRENGTH**

Muscular strength depends on the bulk of the muscle, its contractility, the integrity of its innervation, and its loading conditions. Advanced age and poor nutrition are associated with reduced skeletal muscle mass. Contractility is influenced by the muscle's chemical environment. Derangements of $\text{Ca}^{2+}$, $\text{Mg}^{2+}$, $\text{PO}_4^{3-}$, $\text{K}^+$, $\text{CO}_2$, $\text{pH}$, and perhaps $\text{Fe}^{2+}$ are particularly important to correct. The shorter the inspiratory muscle fiber and the greater its velocity of shortening, the less forceful will be the contraction for any specified level of neural stimulation. The greater the “afterload” faced by the muscle (because of resistive or elastic loading), the less effectively will the muscle contraction perform useful external work. Achieving adequate intravascular volume, ensuring optimal cardiac function, and normalizing hemoglobin concentration help to maintain ample $\text{O}_2$ delivery to these metabolically active tissues. Complete rest of the diaphragm for longer than 24 hours has been associated with the initial stages of atrophy, and after prolonged ventilation, thinning can be detected by ultrasound performed in the zone of apposition of the right hemidiaphragm. Ultrasonically detected impairments of diaphragm thickness, inspiratory thickening ratio, and excursion during active inspiration have been linked to VIDD (Fig. 25-5).
FIGURE 25-5. Two-dimensional and time-based (M-mode) ultrasound tracings of the costal diaphragm originating from the transducer site depicted. When combined with other clinical signs, ultrasonically derived indices of diaphragmatic function during spontaneous efforts hold potential for noninvasively assessing diaphragmatic strength and endurance.

THORACIC CONFIGURATION
However well individual muscle fibers contract, geometric alignment determines how effectively the force generated accomplishes ventilation. When totally flattened, for example, the diaphragm develops tension that tends to pull the ribs inward in an expiratory rather than inspiratory action (see Fig. 25-4). Partially for this reason, acute hyperinflation represents an important impediment to effective ventilation. Spine distortion also impairs the normal mechanical advantage.

MUSCULAR COORDINATION
In generating negative intrathoracic pressure, the inspiratory muscles normally contract synchronously to either displace volume directly or to stabilize the rib cage or abdomen so that the inspiratory actions of complementary muscles work effectively.

Both a stable chest wall and coordinated muscular activity are essential to pump efficiency.

Common Disorders of the Respiratory Pump

CHEST WALL CONFIGURATION
Obesity and Ascites
Massive obesity and ascites are common disorders of chest wall configuration. The stiff chest wall and abdomen burden the muscles of inspiration. However, although the diaphragm must push against the abdominal contents, impairing diaphragmatic descent, the abdomen can provide a fulcrum around which the diaphragm can flare the rib cage outward, expanding its volume. More extensive rib cage displacement may compensate for the reduced caudal displacement of the diaphragm, so that quiet breathing is little compromised. Under the stress of increased ventilation requirements, however, higher tidal volumes are needed, and the elastic work of displacing the chest wall may increase dramatically. With the abdominal contents pushing the diaphragm cephalad, the equilibrium position of the chest wall is displaced to a lower volume, so that functional residual capacity (FRC) tends to fall. In comparison to patients without such chest wall abnormalities, higher levels of PEEP are needed to produce the physiologically effective changes in lung volume that influence oxygenation. This is especially true in the supine position, in which abdominal forces, aided by hydrostatics, push the underside of the diaphragm upward during exhalation. Airway calibers are reduced commensurately as FRC falls and resistance to breathing increases. Impressive gas trapping occurs in the very obese when they transition from the upright to horizontal position. Moreover, the tendencies for hypoxemia and positional desaturation are increased because the patient often breathes from below the “closing volume” of the lung. Therefore, when managing the obese, pregnant, or ascitic patient, special attention must be paid to avoiding belly compression and maintaining positions—usually upright—that minimize gas trapping.

Pleural Effusion and Pneumothorax
Although massive pleural effusion and pneumothorax are not usually considered problems of chest wall configuration, in fact, both can cause dyspnea by this mechanism (see Chapter 8). For example, either may flatten or invert the ipsilateral diaphragm and drive the accessory inspiratory muscles to a hyperinflated position. In this configuration, the individual muscle fibers foreshorten, and the geometry does not permit efficient
inspiratory motion. Thus, a major component of the relief of dyspnea after needle decompression, thoracentesis, or chest tube placement relates to the recovery of an effective mechanical advantage for the diaphragm. Interestingly, although effusions compress the lung, moderately large pleural effusions may not impair the ability of the lung to expand during mechanical ventilation, provided that the surrounding chest wall (rib cage and abdomen) is not stiff. During tidal inflation, rising airway pressure displaces the liquid toward the relatively flexible abdomen, causing tidal lung opening followed by expiratory collapse. Sufficient PEEP prevents this tidal recruitment and may restore lung compliance nearly to normal (see Chapter 8).

**Flail Chest**

Large or painful flail segments may dissipate a portion of the force developed by the intact ventilatory musculature or lead to "splinting," secretion retention, hypoxemia, and ineffective ventilation. Reducing minute ventilation requirements, effective bronchial hygiene, adequate analgesia, restoring FRC by position and PEEP, and providing ventilatory support (noninvasive or invasive) form the cornerstones of treatment until the chest wall stabilizes and the pain recedes (see Chapter 35).

**Kyphoscoliosis**

Kyphoscoliosis distorts the other component of the thoracic shell, the rib cage. This deforming disorder seriously impairs inspiratory capacity, preventing the deep breaths needed for exertion or coughing. In distinction from parenchymal restrictive diseases like pulmonary fibrosis, FRC and diffusing capacity tend to be comparatively well preserved. Initially, the problem is purely one of configuration, but the inability to ventilate and clear secretions effectively can lead eventually to reduced lung compliance, bronchiectasis, and fibrosis. Difficulty increases in proportion to the bony deformity. In scoliosis, for example, serious respiratory problems attributable solely to its mechanical disadvantage are seldom evident until spine angulation exceeds 100 degrees. Muscles that would ordinarily have an inspiratory action can be placed into a neutral or expiratory alignment by severe bony distortion. In addition, the chest cage becomes difficult to deform with tidal breathing efforts. The diaphragm then assumes an especially important role. Severe hypoxemia and cor pulmonale are frequent late complications. For such patients, maintaining the airway free of retained secretions and infection, avoiding obstipation and abdominal distension, treatment of hypoxemia, and ensuring appropriate electrolyte balance and nutrition are keys to effective management.

**MUSCULAR STRENGTH AND COORDINATION**

Many disorders of neuromuscular dysfunction have coexisting elements of secretion retention, atelectasis, aspiration of oral or gastric contents, and sleep-disordered breathing. Nutritional support, assiduous bronchial hygiene, minimization of the breathing workload, avoidance of electrolyte imbalance and consciousness-suppressing drugs, advantageous body positioning, and liberal use of positive airway pressure and ventilation (administered noninvasively, if possible) are general management principles that are applicable across the spectrum of diseases that comprise this category.

Diaphragmatic paralysis and quadriplegia provide complementary but opposing examples of regional muscular weakness. Both disorders present inherent problems of impaired muscular coordination as well as loss of effective muscle bulk and strength.

**Diaphragm**

Predispositions and acute problems observed in the ICU may result in diaphragmatic dysfunction. Pneumonia, surgery, radiation, trauma, and anesthetic complications provide common examples. A paralyzed diaphragm tends to rise rather than fall during the inspiratory half-cycle. Acting as a passive membrane, it then moves in
accordance with the transmural pressure gradient across it. As intraabdominal pressure rises and intrathoracic pressure falls, the diaphragm ascends into the chest. In the chronic setting, unilateral diaphragmatic paralysis only modestly impairs ventilatory capability, with vital capacity falling approximately 20% to 30% from its normal value. Quiet tidal breathing is little affected, and many such patients remain relatively asymptomatic throughout life. Symptoms may only surface under periods of stress or in the presence of a comorbid problem. Although causes of permanent unilateral paralysis can sometimes be identified (e.g., tumor, infection, radiation, or surgery), the origin of most remains unknown.

By contrast, bilateral diaphragmatic paralysis is a devastating illness that usually is idiopathic. These patients must take up the entire ventilatory burden using their accessory muscles. When upright, the expiratory muscles can contract to drive the flaccid diaphragm high into the chest at end-exhalation. When expiratory tone is released, the falling abdominal pressure sucks the diaphragm caudally, thus aiding inspiration. In the supine position, this gravity-dependent mechanism cannot work, and the abdomen moves paradoxically inward during inspiration. Therefore, these patients experience extreme orthopnea and often present with sleep disturbances and headache related to nocturnal CO$_2$ accumulation. Vital capacity shows significant positional variation, falling by more than 30% in the transition from the upright to supine orientation. Many such patients can sustain ventilation spontaneously for hours when upright but need ventilatory support (invasively or noninvasively) for rest periods, especially when sleeping. During the rapid eye movement phase, breathing normally is diaphragm dependent. Positive-pressure ventilation is used most commonly for this purpose, invasively via tracheostomy or noninvasively via a well-fitting mask interface. Poor regional ventilation in dependent areas promotes basilar atelectasis, pneumonitis, and bronchiectasis. Because diaphragmatic function seldom returns, treatment is supportive. Therapy centers on maintaining optimal secretion clearance, keeping the lungs free of infection, and optimizing nutrition.

**Skeletal Muscle Weakness and Paralysis**

The severity of ventilatory problems relating to spinal cord injury relates to the level of the lesion and, to some extent, to the time elapsed since the injury occurred. Ventilatory effectiveness can improve significantly in the initial weeks after the injury, as neural function improves, muscle tone alters the compliance of the chest wall, and any accessory muscles that remain functional build strength. In the usual forms of quadriplegia (levels at or below C5), diaphragmatic function stays well preserved. Depending on level of injury, accessory inspiratory muscles may be compromised, and invariably a variable fraction of expiratory power is lost. Quadriplegic patients and those with acute myopathy often maintain excellent ventilation during quiet breathing but have little or no reserve. Expulsive activity may be severely impaired. For some patients, any pneumonia is potentially life threatening; secretions cannot be raised, and the ventilatory requirement is increased. Maintenance of an upright position and the use of PEEP to avert atelectasis are often helpful. Various techniques and devices are available to assist coughing, including manual compression, chest vibration, airway oscillation, and cough amplifiers that use a biphasic (positive-negative) pressure applied at the airway opening.

Paradoxically, some quadriplegic patients breathe more easily in the recumbent position than when upright. Presumably, the enhanced diaphragmatic curvature of the supine position, as well as the larger area of apposition of the diaphragm to the lower rib cage, improves mechanical efficiency. Like diaphragmatic paralysis, the focus should center on reducing the ventilatory requirement and on keeping the lungs free of infection. For patients who do not have an effective cough, secretion retention and mucus plugging are continual risks. Vital measures are maintenance of optimal nutrition, prevention of aspiration, optimization of bowel motility, prevention of abdominal distension, and prophylactic respiratory therapy and vibropercussion supplemented by assisted coughing (when feasible, indicated, and not contraindicated by abdominal distension, esophageal incompetence,
severe thoracic deformity, spinal fracture, etc.). When some expiratory force can be generated (thoracic cord interruptions), abdominal compression may assist the coughing effort by buttressing the abdomen and allowing intrathoracic pressure to build. Marginal patients often benefit from noninvasive nocturnal ventilatory support. Severely compromised patients who cannot effectively clear the airway with noninvasive aids or who have other airway, lung, or chest wall diseases will require tracheostomy and conventional ventilation.

SUGGESTED READINGS


• Key Points

1. Antibiotic choices should be reassessed on a daily basis, keeping in mind that effective regimens rarely reverse the effects of any infection in less than 48 to 72 hours. Antibiotic choices should be trimmed to the simplest effective combination as clinical response becomes evident and culture data become available.

2. The speed with which an infectious diagnosis is pursued and the invasiveness of the techniques used should parallel the severity of illness. Stable patients with functioning immune systems and good physiologic reserves require less aggressive diagnostic approaches, whereas critically ill, highly vulnerable, and fragile patients require rapid, definitive diagnosis.

3. When several equally effective alternatives exist to treat the same infection, choose the combination with the best side effect and cost profile. Oral therapy and parenteral dosing of a long-acting antibiotic given on an infrequent schedule are usually the best methods of reducing antibiotic costs.

4. Antibiotics should be selected based on culture results, if available, and on microscopic examination of body fluid specimens if not. In the absence of diagnostic material, the clinical history and presumed site of infection should be the primary determinants of antibiotic selection.

5. For the unstable, infected, or septic patient, broadspectrum empiric antibiotic therapy should be instituted after obtaining appropriate cultures. As a rule, for such patients, it is best initially to give too many rather than too few antibiotics—second chances to choose the appropriate therapy may not arise.

OVERVIEW

Infection may be suspected on the basis of localizing signs (e.g., swelling, erythema, wound discharge) or localizing symptoms (e.g., pain, dyspnea, cough) but commonly is considered on the basis of fever or leukocytosis. Fever afflicts at least half of all patients during their stay in the intensive care unit (ICU) and often is an important clue to the presence of infection. The magnitude and pattern of fever, typically defined as a temperature exceeding 101°F (38°C) to 101.4°F (38.5°C), are often accorded undue significance; fever characteristics actually have little diagnostic value. It is essential to recognize that not all fever is due to infection. Several diseases as deadly as disseminated infection can induce fever. Prominent among them are heat stroke, neuroleptic malignant syndrome, and the endocrine disorders of hyperthyroidism, adrenal insufficiency, and pheochromocytoma. Noninfectious causes of febrile syndromes are discussed in detail in Chapter 28.

For some patients, diagnosis of infection is difficult because both localizing and generalized signs are unimpressive. Patients infected with human immunodeficiency virus (HIV) often have minimal tissue inflammation when infected. Elderly patients and patients with hypothyroidism and renal failure often have reduced fever responses compared to younger patients. Both neutropenia and immunosuppressive drug therapy tend to reduce the local response to infection, making erythema, pain, swelling, and pus formation less likely.

CATEGORIES AND CAUSES

Three categories account for most infections seen in the ICU: primary bacterial infections that prompt admission (e.g., pneumonia, urinary tract infection [UTI], meningitis); nosocomial infections (e.g., catheter-related sepsis,
nosocomial pneumonia); and infections of the immune-compromised host. The broad topic of infection cannot be addressed comprehensively in a single chapter of reasonable length; therefore, the discussion that follows focuses on the most common and serious infections occurring in the ICU. Patient characteristics profoundly influence the likely site of infection and the organisms most commonly responsible. The selection of antimicrobials must take allergies and organ dysfunctions into account. Furthermore, individual hospitals have different spectra of bacteria causing a particular clinical syndrome, and even within a single hospital antibiotic susceptibility can vary widely among units. Therefore, practitioners must have a thorough knowledge of the patient being treated, the likely pathogens, and the antimicrobial susceptibility pattern of the hospital in which they practice.

Antimicrobial options are constantly evolving. In recent years, for example, entirely new antibiotic categories have been exploited and better tolerated formulations of long-established drugs have been commercially released. In the former category are drugs directed at organisms resistant to most standard agents, such as linezolid, daptomycin, and quinupristin-dalfopristin for methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus*. Others include nontraditional antifungal agents, such as caspofungin for invasive *Aspergillus* and *Candida* infections. Nephrotoxicity of traditional amphotericin desoxycholate has been attenuated by its lipid complex, cholesteryl sulfate complex, and liposomal variants. Voriconazole, a modified triazole, now offers a well-tolerated alternative to amphotericin that can be given orally as well as parenterally in the treatment of aspergillosis. Modifications within well-established antimicrobial categories have extended their spectra and/or limited their side effects. For example, fluoroquinolones (e.g., levofloxacin, gatifloxacin, and moxifloxacin) offer potent competition to traditional drugs in the treatment of typical and atypical pneumonia. Allergic sensitivity, renal insufficiency, hepatic dysfunction, bleeding tendency, or other vital organ dysfunctions may restrict options, but almost always, there exist more than one potentially effective antimicrobial combination. Suggestions that follow for antibiotic therapy are based on the most common pathogens and their usual susceptibility patterns while considering the frequency and severity of side effects and ease and cost of administration. “Broad-spectrum” effectiveness is both a luxury and a liability, as the desire to cover a large number of potential pathogens comes at a high price. Indiscriminate use of broad-spectrum antibiotics is rapidly producing multidrug-resistant bacteria. MRSA and penicillin-resistant *Pneumococcus* are now pandemic. New and menacing pathogens such as multiresistant *Enterococcus* and *Acinetobacter* are recognized with increasing frequency. Unless patterns of antibiotic use change, it is likely such infections will grow in importance. Antibiotics are the only class of drugs that, when misused, can injure not only the patient being treated but nearby patients and those admitted to the ICU in the future. For example, the routine use of vancomycin to treat diarrhea or to cover for Gram-positive pathogens may inadvertently “select out” organisms resistant to this useful drug. These highly resistant organisms then lurk in the ICU, ready to infect subsequent patients.

**Urinary Tract Infections**

**Pathogenesis**

The urinary tract, the most common site of ICU infection, accounts for almost 40% of all infections. Although UTIs usually are inconsequential, the mortality rate for a bacteremic UTI approaches 30%. Risk factors for UTI include presence of a urinary catheter, female gender, diabetes, and advanced age. Colonization of urinary catheters occurs at a rate of about 5% to 10% per day, and most ICU-acquired UTIs occur in such colonized patients. Presumably, the colonized catheter permits retrograde passage of pathogenic bacteria into the bladder where they proliferate. Urinary catheter composition (Teflon rather than rubber) may reduce the infective hazard; however, there is no evidence that routine changing of the catheter or external application of antibiotic ointment decreases risk. Keys to preventing nosocomial UTI are sterile catheter insertion, early catheter removal, and maintenance of a closed drainage system.
**Diagnosis**

The diagnosis of UTI is all but certain when greater than $10^5$ bacteria/mL are isolated from culture of freshly collected urine. This level of bacteriuria correlates well with the presence of more than one organism per high-power field of unspun urine. Unfortunately, fewer bacteria do not exclude the presence of infection. True infections have been documented with colony counts as low as $10^2$/mL. *Escherichia coli*, the most common bacterial isolate, occurs in about 30% of UTIs. *Enterococcus* and *Pseudomonas* are each recovered about 15% of the time in the ICU population. *Klebsiella* and *Proteus* species represent less common isolates. Contrary to previous teaching, in many cases, pure cultures of *Staphylococcus epidermidis* represent infection, not contamination. In the absence of frank pyuria or quantitative culture data, it is difficult to differentiate colonization from infection in critically ill patients with indwelling catheters. In the tenuous patient with bacteriuria, it is probably best to err on the side of brief, organism-directed antibiotic therapy. For more resilient patients in the ICU, treatment of asymptomatic bacteriuria may be deferred safely.

*Candida* species are commonly recovered from urine. The choice of therapy for isolated candiduria should be based on a clinical judgment regarding whether the patient is "colonized" or "infected." Unfortunately, few reliable signs distinguish these conditions. A clinical picture of sepsis, with recovery of *Candida* from blood cultures as well as urine, suggests disseminated infection that should be treated with intravenous antifungals such as amphotericin B, fluconazole, or caspofungin. Conversely, finding small numbers of yeast in an asymptomatic patient with an indwelling urinary catheter rarely requires systemic treatment (except expedited removal of the catheter). The most difficult situation occurs when large numbers of yeast or clumps of hyphal forms are found in the urine of an asymptomatic patient or a patient with only modest fever. Although suggestive of invasive infection, such patients usually respond promptly to fluconazole (oral or intravenous), especially if the urinary catheter can be removed. Without evidence of infection elsewhere, parenteral amphotericin B probably should be reserved for immunocompromised patients or those with limited physiologic reserves. Bladder irrigation with amphotericin B is time consuming, expensive, of uncertain benefit, and confounding to accurate assessment of urine output. Fluconazole has all but eliminated bladder irrigation.

Pyocystis, an invasive infection of the bladder wall, may complicate oliguria or anuria, especially in patients requiring hemodialysis. In this setting, reduced urine flow allows bacteria to proliferate to massive numbers within the bladder. For oliguric patients with obscure fever, the bladder should be catheterized and the urine sediment examined. In the appropriate setting, murky, turbid, culture-positive urine establishes the diagnosis.

**Treatment**

The aggressiveness of therapy should parallel the clinical severity of the acute syndrome and the underlying illness. As a rule, presumed UTIs should be treated aggressively because patients in the ICU often have impaired immunity (diabetes, HIV infection, immunosuppressive therapy), numerous indwelling devices (e.g., vascular catheters, prosthetic heart valves, pacemakers), and marginal physiologic reserves. The treatment of UTI includes the promotion of urine flow and drainage, removal of urinary catheters (when feasible), and antibiotic therapy. Not all patients with bacteriuria require prolonged courses of expensive, broad-spectrum, intravenous antibiotics. Otherwise, stable immunocompetent patients can be treated successfully using enteral antibiotics (e.g., ampicillin, trimethoprim-sulfamethoxazole, quinolones). Oral
therapy is not appropriate for septic patients or patients with obstructive uropathy or a focal complication (e.g., renal abscess). The need for two drug coverage of pseudomonal infections in nonimmunocompromised patients is uncertain, but two drugs effective against *Pseudomonas* should be given to patients with abnormal immunity. (These include intravenous aminoglycosides and antipseudomonal penicillins, fluoroquinolones, or third-generation cephalosporins.) If *Enterococcus* or *Staphylococcus* is deemed likely (based on the urine Gram stain or culture), vancomycin probably should be first-line therapy. Rarely, when the infection is life threatening and the possibility of vancomycin resistance is high, linezolid is an appropriate choice. Urine concentrations of renally excreted antibiotics often are dramatically higher than those used in sensitivity testing; therefore, UTIs often can be cured using an antibiotic to which the bacteria are found to be “resistant” *in vitro*. Because drainage bags provide important pathogen reservoirs, manipulations of the closed drainage system should be undertaken only when necessary and conducted with sterile technique. Furthermore, drainage bags should not be raised above the level of the bladder, as often occurs during patient transport. Doing so, even briefly, produces urinary stasis and promotes retrograde flow of potentially highly contaminated urine.

**Pneumonia**

**Pathogenesis**

Pneumonia-producing organisms usually enter the lower respiratory tract in aspirated upper airway secretions. Hematogenous seeding is a much less common mechanism. Unless the inoculum is very large, glottic closure, cough, and mucociliary clearance normally provide an effective mechanical defense (Table 26-1). Even when mechanical barriers fail, infection usually is averted by effective cellular (neutrophil and macrophage) and humoral immunity (antibody secretion). Unfortunately, both mechanical and immune defenses are jeopardized commonly in critically ill patients, even in those without a recognizable immune deficiency. Common conditions that allow proliferation of organisms leading to pneumonia are listed in Table 26-2. The organism causing pneumonia is highly dependent on where the infection was acquired and on individual patient characteristics.

**Table 26-1. Conditions Promoting Lung Inoculation**

<table>
<thead>
<tr>
<th>Aspiration</th>
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<tbody>
<tr>
<td>Depressed consciousness</td>
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<tr>
<td>Swallowing disorders</td>
</tr>
<tr>
<td>Nasogastric and tracheal tubes</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Hematogenous seeding (e.g., endocarditis)</th>
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<tr>
<td>Bacteremia</td>
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<td>Fungemia</td>
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<table>
<thead>
<tr>
<th>Infected aerosols</th>
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<tr>
<td>Contaminated ventilator tubing and humidifiers</td>
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</table>
**Diagnosis**

In the community, a patient with acute onset of fever, dyspnea, chest discomfort, and cough productive of purulent sputum is likely to be suffering from bacterial pneumonia. Leukocytosis with a predominance of neutrophils and distinct (new) infiltrate(s) on chest radiograph are strong supporting data. Lobar pneumonias often have detectable air bronchograms in the zone of infiltration (Fig. 26-1). Sputum that demonstrates an overwhelming proportion of neutrophils, intracellular organisms, and the predominance of a single morphologic bacterial form further strengthens the case. Finally, the diagnosis is established unequivocally by recovering the same organism from blood and sputum or pleural fluid cultures. The presentation is not always classic, even with community-acquired pneumonia: fever may be mild, infiltrates may be subtle, and self-medication with antibiotics often obscures a bacteriologic diagnosis.

![Image of chest X-rays and CT scan showing air bronchograms in the setting of pneumonia](image)

**FIGURE 26-1. Air bronchograms in setting of pneumonia.** Air bronchograms are usually best detected by CT scanning.

<table>
<thead>
<tr>
<th>Table 26-2. Conditions Favorable to Proliferation of Microorganisms in Lung</th>
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<tbody>
<tr>
<td>Impaired immunity</td>
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<tr>
<td>Parenchymal necrosis</td>
</tr>
<tr>
<td>Malnutrition</td>
</tr>
<tr>
<td>Steroids/cytotoxic drugs</td>
</tr>
<tr>
<td>Chronic alcohol abuse</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Secretion retention</td>
</tr>
<tr>
<td>Atelectasis</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Obstructive lung disease</td>
</tr>
<tr>
<td>Neuromuscular weakness</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
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<tr>
<td>Viral infections</td>
</tr>
</tbody>
</table>

In the ICU, making a correct clinical diagnosis of pneumonia can be difficult for several reasons. Fever and leukocytosis are nonspecific, and patients often have several potential nonpulmonary sites to explain these findings. In addition, the radiographic infiltrates that suggest pneumonia are mimicked by atelectasis, aspiration pneumonitis, pulmonary embolism and infarction, pleural effusion, and pulmonary edema (Fig. 26-1).
Computed tomography (CT) sharpens discrimination but may not settle the issue. An elevated level of procalcitonin, a readily measured biomarker, strongly suggests bacterial (as opposed to viral) pneumonia. Finally, widespread use of antibiotics inhibits the ability to recover a single pathogenic organism, and even when sputum cultures are positive, small numbers of colonizing bacteria are usually recovered.

**FIGURE 26-2.** Lobar atelectasis without air bronchogram (*left*) suggests occlusion of a lobar bronchus (e.g., by mucus plug). Note the closer spacing of ipsilateral ribs (*blue arrow*) and mediastinal shift along with compensatory contralateral lung expansion (*red arrow*). The presence of an air bronchogram (*yellow arrow, right*) in conjunction with lobar volume loss indicates collapse with an open lobar passage and argues against the value of therapeutic bronchoscopy.

**Causative Organisms**

The organisms causing pneumonia differ dramatically, depending on site of acquisition—community versus hospital. Common causes of community-acquired lobar pneumonia and their clinical associations are shown in Table 26-3. In the community, streptococci, especially *Pneumococcus*, and *Haemophilus influenzae*, *Mycoplasma*, and viruses are the most common pathogens in otherwise “healthy” adults. Many underlying conditions vary this spectrum, however. In addition to the organisms already mentioned, patients with alcoholism, diabetes, or heart failure are predisposed to infections with *Klebsiella*, *Legionella*, enteric Gram-negative rods, and *Staphylococcus*. When aspiration is likely (e.g., alcoholism, drug abuse, esophageal disorders), *Bacteroides* and other anaerobes are potential culprits. *S. aureus* frequently is recovered from patients with “postinfluenza” pneumonia, and *Pseudomonas* species and *Staphylococcus* are common etiologic organisms among patients with cystic fibrosis. In fact, staphylococcal disease including MRSA is now frequently encountered in patients with severe community-acquired pneumonia. Pneumonia acquired in chronic nursing care facilities or within 3 weeks of hospital discharge is likely to be caused by organisms usually recovered in hospital-acquired infections.

For pneumonias that develop after the first few days in the ICU, a different, hospital-specific spectrum predominates. Such infections are frequently polymicrobial. Gram-negative rods (*Pseudomonas aeruginosa*, *Klebsiella* species, *Enterobacter* species, *Acinetobacter* species, *E. coli*, *Proteus*, and
Serratia) cause approximately 50% of all ICU pneumonias. Which Gram-negative organism predominates at a given hospital has a great deal to do with antibiotic pressure placed on its environment. Acinetobacter, for example, represents a significant threat in some hospitals, but by no means all. S. aureus causes another 10% to 20% of infections and its incidence appears to be higher or rising in many ICUs. The predominance of Gram-negative rods and Staphylococcus seen in the hospitalized patient is explained partially by the rapid rate at which the oropharynx of the critically ill patient becomes colonized. Almost all critically ill patients are colonized with nonnative Gram-negative bacteria (many of which are antibiotic resistant) by the third hospital day.

All too often, a specific pathogen cannot be identified, despite good sampling methods and symptoms compatible with acute pneumonia. Mixed polymicrobial aerobic/anaerobic infections, Mycoplasma, Chlamydia, Legionella, and viral agents become more likely candidates under these conditions. Although fungal pneumonia (Candida/Torulopsis species, Aspergillus, or Mucor) must be considered in the neutropenic (<500 neutrophils/mm³), diabetic, or severely debilitated patient, it occurs only rarely in immunocompetent ones. When fungal lung involvement occurs in the immunocompetent patient, it usually is the result of hematogenous seeding with Candida in a predisposed host. For some patients with chronic destructive lung diseases (e.g., chronic obstructive pulmonary disease [COPD] or healed cavitary tuberculosis), Aspergillus can produce a primary invasive pneumonia.

Patients infected with HIV present a unique set of problems. When the CD4 T-cell counts are normal, patients infected with HIV are susceptible to the same organisms as any other adult in the risk categories outlined in Table 26-3. As the CD4 count declines (especially as it falls below 200 cells/mm³), the spectrum of infecting organisms broadens. Although routine bacterial pathogens still predominate, Pneumocystis carinii (jiroveci), Mycobacterium tuberculosis, atypical mycobacteria, and fungal infections become more likely. There is a rough correlation between the CD4 count and the infecting organism, but the linkage is not sufficiently strong to forgo detailed evaluation and broad coverage. Potential pathogens also are influenced by the prior use of prophylactic therapy. Oral trimethoprim-sulfamethoxazole prophylaxis, for example, has dramatically reduced the incidence of Pneumocystis and Toxoplasmosis infections.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Likely Organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy adult</td>
<td>S. pneumoniae, Mycoplasma, viruses (e.g., influenza), Chlamydia, H. influenzae</td>
</tr>
<tr>
<td>Predisposed to aspiration</td>
<td>S. pneumoniae, Bacteroides, oral anaerobes</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>Esophageal disease</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td>Alcohol and drug abuse</td>
<td></td>
</tr>
</tbody>
</table>
Recent dental work

Chronically ill

All organisms listed for healthy adult plus *Klebsiella* species, enteric Gram negatives, *Legionella*, *S. aureus*, *Branhamella* species.

Diabetes
COPD
Heart failure
Low-dose steroids

Postinfluenza

*S. pneumoniae*, *S. aureus*, *H. influenzae*

Cystic fibrosis

*S. aureus*, *Pseudomonas* species.

AIDS or HIV with CD4 < 200

*P. carinii*, *S. pneumoniae*, *H. influenzae*, *M. tuberculosis*, fungal infection (geographic predilection)

Neutropenia

All organisms listed for chronically ill plus *Aspergillus*, *Mucor*, and *Candida*

Regardless of the patient substrate, the choice of initial therapy for a bacterial pneumonia is always accompanied by some uncertainty, even in the presence of a Gram stain “typical” of a specific organism. Historical features can help immensely in sorting through the diagnostic possibilities. For example, the sudden onset of chills, pleurisy, rigors, and high temperature are characteristic features for community-acquired *Pneumococcus* in a young adult. On the other hand, such findings may be inconspicuous in an older person, in whom confusion or stupor often predominate. A history of seizures, drug abuse, alcoholism, or swallowing disorder focuses attention on aspiration. Recent travel history, occupational or recreational exposure, and concurrent family illnesses can help diagnose an unusual organism (Table 26-4). In the absence of intrinsic cardiac conduction abnormality or intense β-blockade, a pulse rate that fails to rise in proportion to fever (pulse-temperature dissociation) suggests an “intracellular pathogen” such as *Legionella*, *Rickettsia*, *Mycoplasma*, Q fever, psittacosis, virus, or tularemia. *Mycoplasma* often has accompanying pharyngitis, myringitis, or conjunctivitis. Contrary to popular teaching, extrapulmonary symptoms (diarrhea, central nervous system disease) are no more common in Legionnaires disease than in other bacterial pneumonia.

### Table 26-4. Clues to Uncommon Causes of Pneumonia

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Historical Clue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histoplasmosis</td>
<td>Excavation, bird exposure, Ohio Valley and midwestern USA</td>
</tr>
<tr>
<td>Coccidiomycosis</td>
<td>Travel to southwestern United States, Central California</td>
</tr>
<tr>
<td>Tularemia</td>
<td>Tick bite or exposure to skinned animals</td>
</tr>
</tbody>
</table>
Unlike community-acquired pneumonia, nosocomial pneumonia offers few historical clues to diagnosis. Occasionally, however, a skin rash, gingival disease, or purulent sinus drainage helps narrow the possibilities. Numerous classic radiographic features have been described, including lobar consolidation without air bronchograms (central obstruction), bulging fissures (Klebsiella), infiltrate with ipsilateral hilar adenopathy (histoplasmosis, tularemia, tuberculosis), widespread cavitation (Staphylococcus, Aspergillus), and sequential progression to multilobar involvement (Legionella). These findings are not sufficiently consistent, however, to be of real value in confirming the diagnosis.

**Diagnostic Techniques**

Although the history provides clues to the etiologic organism, laboratory studies are the cornerstone of the workup. Leukopenia often results from overwhelming infections, particularly those that are due to Staphylococcus, Pneumococcus, or Gram-negative organisms. A differential count that is not significantly left shifted suggests the possibility of virus, Mycoplasma, or Legionella. Cultures of blood and pleural fluid (when present) must be obtained, and if positive, they are the most convincing evidence of a causative organism. Unfortunately, such specimens are usually nondiagnostic, even in seriously ill patients, and sampling of pulmonary secretions becomes the primary diagnostic modality.

The aggressiveness of the diagnostic evaluation should parallel the severity of the illness. In an otherwise healthy young person with a lobar pneumonia and good oxygenation, empiric therapy or treatment based on Gram stain alone is acceptable. For the septic, profoundly hypoxic, or immunocompromised patient, however, a more systematic evaluation is often prudent. When performed correctly, stain and culture of pulmonary secretions or alveolar lavage fluid remain the most likely techniques to yield a diagnosis. For patients with severe community-acquired pneumonia, high-quality sputum often is obtained immediately after endotracheal intubation because forceful coughing and suctioning at this time often yield copious lung secretions not yet contaminated by ICU colonization. Expectorated sputum is appropriate for analysis and culture only if there is a high ratio of inflammatory to epithelial cells. Apart from the Gram stain, direct immunofluorescent antibody staining for Legionella and tuberculosis is another useful method for processing the expectorated sample that can yield an immediate, but presumptive, diagnosis. Inhalation of a hypertonic aerosol, particularly if given via an ultrasonic nebulizer, can stimulate a productive cough in patients otherwise unable to expectorate. When adequate sputum is not expectorated, nasotracheal...
Suctioning can be helpful. Transtracheal aspiration has been all but abandoned with wide availability of fiberoptic bronchoscopy. Urinary antigen testing is highly significant for both pneumococci and legionella species.

Properly performed on well-selected patients, fiberoptic bronchoscopy is a valuable technique for evaluation of pneumonic infection. In general, bronchoscopic procedures should be reserved for those who are seriously ill, immunocompromised, or unresponsive to conventional therapy. The safety and ease of bronchoscopy are facilitated by the presence of an endotracheal tube. When a decision is made to perform bronchoscopy, bronchoalveolar lavage and protected brush sampling from the involved region are both reasonable alternatives. Of these, lavage methodology is perhaps more popular, as it is easier, and the protected brush seldom conflicts with or adds to its accuracy. If the lavage specimen yields a predominance of polymorphonuclear leukocytes and more than $10^3$ to $10^4$ organisms/mL are isolated, infection with the recovered organism is likely. Fewer bacteria suggest an active infection but also may be seen with a partially treated bacterial pneumonia. Blind suctioning, conducted with or without lavage through a wedged catheter (“mini-BAL”), can be performed proficiently by respiratory therapists or trained nurses. In the setting of diffuse pneumonia, this is a low-cost and generally effective sampling option. Only bronchoscopy, however, offers the directed sampling so often necessary.

Performing transbronchial biopsies to obtain tissue for histologic examination and/or culture is more hazardous in mechanically ventilated patients. Moreover, empirically chosen antibiotics are usually effective in addressing potential pathogens in patients who are immunocompetent. Although not often performed because of the risk of pneumothorax, transbronchial biopsy may be attempted when tissue recovery is essential, oxygenation can be well maintained, and coagulopathy is not present. In this setting, the only diagnostic alternatives are open or thoracoscopic lung biopsy. (The latter may not be feasible because of altered anatomy, high ventilation requirements, or refractory hypoxemia.) The risk of developing a pneumothorax while supported by the mechanical ventilator must be balanced against the potential yield and the clinician’s ability to promptly recognize and evacuate the air leak. (Note that the incidence of pneumothorax approaches 100% after open lung biopsy.) In addition, there are situations in which a diagnosis can be made only by tissue biopsy. Open lung biopsy is rarely necessary for patients with intact host defenses, and the value in even compromised hosts is arguable. Transthoracic needle aspiration often yields an adequate specimen but exposes the patient to attendant risks of pneumothorax and bleeding.

The optimal diagnostic evaluation of a pneumonic process for patients infected with HIV continues to evolve. For patients with normal or minimally reduced CD4 counts, mild to moderate illness, and a history and examination compatible with acute bacterial pneumonia, empiric antibacterial therapy after obtaining cultures is reasonable. For patients with reduced CD4 counts, progressive dyspnea, nonproductive cough, elevated lactic dehydrogenase (LDH), and a radiograph with an interstitial or ground-glass pattern, empiric therapy for *Pneumocystis* and close observation may be reasonable. (This is especially true in the absence of prior *Pneumocystis* prophylaxis.) For patients with low CD4 counts, severe hypoxemia, uncharacteristic chest X-ray infiltrates, or an unusual exposure history, early bronchoscopy is the most prudent option. When bronchoscopy is performed, bronchoalveolar lavage alone often is not sufficient; fungal infections, tuberculosis, and even *Pneumocystis* are missed at an unacceptable rate without transbronchial biopsy. Because of the wide variety of potential radiographic presentations of tuberculosis, it probably is wise for all patients with HIV symptoms and acutely abnormal chest radiographs to be placed in respiratory isolation until a diagnosis of tuberculosis can be excluded reasonably.
Treatment

Nutritional, fluid, electrolyte, and oxygen support of the patient with bacterial pneumonia are not controversial and are applied universally. The initial choice of antibiotic(s) must be guided not only by the nature of the suspected organism but also by the severity of the illness and underlying patient factors. Thus, although treatment should be directed as specifically as possible for patients who are only moderately ill, the initial therapy of a fragile patient with serious illness should include broad-spectrum coverage. Pruning of the antibiotic regimen occurs when the specific causative organism and its likely sensitivity are confirmed. It makes sense to give the chosen antibiotics as quickly as is feasible. There is little margin for error in critically ill patients with pneumonia; however, one can never treat all potential pathogens. Holes in coverage always exist, and there is almost always more than one acceptable antibiotic combination. The selection of antibiotic therapy represents a calculated bet against the most likely organisms.

Recognizing the imprecision of the following descriptions, otherwise healthy patients with community-acquired pneumonia caused by an unknown organism who exhibit little systemic toxicity can be treated initially with either ampicillin or a macrolide antibiotic, such as azithromycin or clarithromycin. Macrolides, fluoroquinolones, and doxycycline are good options when atypical organisms are suspected. If the same patient appears toxic, reasonable initial treatments include ceftriaxone with or without azithromycin, levofloxacin, or moxifloxacin with ceftriaxone or an extended-spectrum penicillin. The following caveats apply: if postinfluenza pneumonia (Staphylococcus) is suspected or if the patient is from a geographic region with a high prevalence of penicillin-resistant pneumococci, the addition or substitution of vancomycin should be considered. For patients with a high likelihood of aspiration, clindamycin alone and amoxicillin-clavulanate with metronidazole represent good initial choices. Community-acquired pneumonia in a patient with HIV was discussed earlier.

Because a second chance to institute the correct therapy cannot be guaranteed, broad empiric coverage is necessary for the toxic patient with nosocomial pneumonia. Recognizing that many toxic-appearing patients will not have pneumonia documented, nonetheless, coverage in this situation must include enteric Gram-negative rods (including multiresistant organisms), Streptococcus (including penicillin-resistant organisms), and Staphylococcus (including MRSA). Important clues to etiology can be gleaned from knowledge of the patient's recent antibiotic treatment, the resident flora of the ICU, the patient's underlying illnesses, environmental exposures, and available culture data. Yet, in the majority of instances, therapy must be initiated empirically. Regardless of the appearance of the Gram stain, initial therapy for critically ill patients should include a coverage for multiresistant Gram-negative bacilli, such as an extended-spectrum penicillin plus an aminoglycoside or appropriate fluoroquinolone (e.g., ciprofloxacin) or a third-generation cephalosporin (e.g., ceftazidime) plus an aminoglycoside or fluoroquinolone. For patients predisposed to staphylococcal infection (e.g., recent influenza, neutropenia, institutional prevalence, or a suggestive sputum Gram stain), vancomycin represents first-line coverage. A fluoroquinolone, macrolide, or doxycycline should be added if there is an “atypical” clinical or radiographic presentation or if fever persists despite usual therapy.

Highly resistant bacteria can be transferred between patients in the ICU, necessitating measures to decrease cross-contamination. Careful handwashing or use of a bactericidal lotion between patient contacts dramatically decreases the risk of nosocomial infection. Use of gloves does not diminish the need for handwashing, and it is essential that gloves be changed between patient contacts. Whenever suctioning intubated patients, gloves should be worn on both hands to prevent staff acquisition and transfer of pathogens, including herpes viruses.
One pneumonic infection that deserves special discussion is pulmonary tuberculosis. Although patients may be admitted to the ICU with signs and symptoms typical of pulmonary tuberculosis (cavitary apical infiltrates, cachexia, fever), the presentation is often subtle. Tuberculosis in the ICU can take on almost any clinical or radiographic presentation. Cavitary lung disease is only marginally more common than other frequently encountered variants: punctate interstitial infiltrates ("miliary pattern"), lobar pneumonia, “empyema,” lung nodule, or diffuse bilateral infiltrates compatible with acute respiratory distress syndrome (ARDS). When the suspicion of tuberculosis is high, respiratory isolation should be instituted as quickly as possible and maintained until firm evidence suggests that the likelihood of contagion is low. (This is accomplished simply by examining two or more good-quality sputum smears for acid-fast organisms.) The implications of missing a case of tuberculosis are enormous: potential death or disability of the infected patient and transmission of infection to the staff and other nearby immunocompromised patients.

**Viral Pneumonia**

Certain forms of viral pneumonia occur with distressing frequency in severely immunocompromised patients (e.g., CMV in transplant recipients). Although rhinitis, sinusitis, laryngitis, and other familiar manifestations of the “common cold” afflict most persons one or more times per year, viral disease rarely extends to the alveolar level in immunocompetent adults. Yet, certain classes of organism—notably adenovirus, influenza, varicella zoster, and in the recent past the coronaviruses responsible for severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS)—can cause devastating illness in exposed individuals who are vulnerable. These diseases generally present with a diffuse bronchopneumonia or ARDS. In addition to general supportive measures applied to patients in respiratory failure, isolation is required and viral antimicrobials should be considered. For example, acyclovir (varicella), rimantadine (influenza), and ribavirin (adenovirus) each offer modest benefit when used in timely fashion in well-selected cases. Perhaps the most important aspect in the management of these pneumonias is to take appropriate measures to prevent the spread of these contagious diseases to health care workers and to the patients they treat. The importance of such precautions was dramatically emphasized in the high incidence of illness among physicians during the SARS outbreak of 2003. When an appropriate vaccine is available for a contagious disease (e.g., influenza), immunization of exposed individuals is prudent.

**Empyema and Parapneumonic Effusions**

**Definition**

Small amounts of pleural fluid routinely accumulate adjacent to pneumonias, and such collections are termed “parapneumonic effusions.” Most parapneumonic effusions are intermediate or even transudative in nature (protein <3.5 g/dL or 50% of the serum level; LDH < 200 U/dL or 60% of the serum level), freely flowing, and self-limited. The term “complicated parapneumonic effusion” has been applied to effusion with loculations, the characteristics of which fall somewhere between an uncomplicated, self-resolving parapneumonic effusion and an empyema. Usually exudative by protein and LDH criteria, leukocyte counts usually are less than 20,000/mm$^3$, and glucose levels fall between the serum value and 20 mg/dL. The pH of such effusions is commonly regarded as a discriminator of the need for drainage, but its discriminating value is often limited. Although it is true that the lower the pH, the more likely a pleural effusion is to have characteristics of an empyema (see following), the pH alone neither makes the diagnosis of an empyema nor dictates a particular course of action. Effusions with a pH less than 7.0 (with a normal arterial pH) are likely to be empyemas and are likely to require drainage by tube thoracostomy, but such associations are
not always valid. An acidic, thin, clear, or slightly cloudy sterile fluid does not necessarily require tube thoracostomy, whereas a thick, viscous, protein- and leukocyte-rich effusion would require thoracostomy, regardless of fluid pH. As a general rule, freely flowing effusions that separate the lung from the chest wall by more than 1 cm on a lateral decubitus film, those that are loculated, and those that do not flow freely, should be sampled and/or drained (Fig. 26-3). The existence of parietal pleural thickening documented on a contrast-enhanced CT scan suggests an intense inflammatory response and probable empyema. The ease and safety of thoracentesis in the ICU may be enhanced by using ultrasound localization (see Chapter 11).

FIGURE 26-3. Ultrasonic (A) and CT (B) images of complicated pleural effusion and empyema.
Though less precise than CT, bedside ultrasound is convenient and may be definitive. Both are helpful prior to interventional procedures such as chest tube placement.

Empyema is defined as an effusion with organisms detected by Gram stain or as “pus” in the pleural space. Unfortunately, observers vary widely in their definition of pus. The diagnosis of empyema is not made by laboratory testing, and there are no specific laboratory cutoff values for what constitutes an empyema. Many empyemas do not have microorganisms visible on Gram stain examination, and not all empyemas grow bacteria in culture, perhaps because antibiotic therapy has already been administered or because the responsible organism is inherently difficult to isolate (e.g., anaerobes). If infected with bacteria, especially anaerobic bacteria, the odor of an empyema is memorable. Generally, accepted characteristics of an empyema are grossly cloudy or opaque appearance and thick, viscous character because of high levels of protein and leukocytes. Certainly, not all infected pleural fluids are thick. Yet, it is the physical characteristics of the fluid that make empyema important to diagnose and treat appropriately. Intrapleural streptokinase can reduce the need for pleural decortication if used early in the clinical course and is often helpful later when tube drainage slows and pockets remain. Intrapleural streptokinase is associated with a low risk of either allergic reaction or systemic coagulopathy. Several types of pleural effusions can mimic an empyema: chylothorax, rheumatoid effusion, tuberculous effusion, and resolving hemothorax all can have the thick, turbid appearance characteristic of bacterial empyema.

The clinical presentation of empyema can be subtle. It is not uncommon for elderly or debilitated patients to have empyema as the primary cause of or cocontributor to chronic wasting illness. The diagnosis should be suspected in patients with unresolving or hectic fever and pleural effusions that do not improve with
antibiotic therapy. Empyema becomes more likely if the suspect fluid collection is adjacent to pneumonia. Because ICU chest films are often taken supine or semiupright, the classic “layering” of an effusion can be missed. Although decubitus views and pulmonary ultrasound enhance the likelihood of finding an effusion, CT currently is the most definitive way to confirm a free or loculated fluid collection, especially if small or loculated. For febrile or frankly septic patients, especially those with an underlying pneumonia, the search for an empyema is reasonable.

**Therapy**

Three basic principles apply to treating empyema: early diagnosis, appropriate antibiotic therapy, and thorough drainage. Of these, drainage is most important. Because there are no radiographic or physical examination features to distinguish an empyema from a routine pleural effusion, thoracentesis is required. Prompt diagnosis minimizes both early (sepsis and respiratory failure) and late complications (fibrothorax and debilitation). When turbid, viscous, pleural fluid (especially if foul smelling) is obtained at thoracentesis, cultures for aerobic and anaerobic bacteria, tuberculosis, and fungi should be sent. In addition to routine cell counts and chemistry analysis, it is prudent to obtain triglyceride and cholesterol levels to exclude a diagnosis of chylothorax, which can have an empyema-like (turbid) appearance. (Effusions caused by rheumatoid disease also can have a similar appearance.) The pleural fluid should be Gram stained and sputum and blood cultures obtained. Antibiotic coverage should be chosen initially on the basis of the Gram stain and then fine-tuned by culture results. The usual etiologic suspects for pneumonia also cause empyema (Streptococcus pneumoniae, H. influenzae, anaerobic mouth flora); however, staphylococci also should be covered. Antibiotics alone are insufficient; prompt insertion of a thoracostomy tube(s) of sufficient caliber to completely drain the pleural space is almost always indicated. Several tubes may be required to fully drain the collection when the fluid is multiloculated. Chest CT guidance can be invaluable in guiding placement. Effusions that do not resolve with antibiotics, tube thoracostomy, and intrapleural thrombolytics may require exploration and drainage by thoracotomy or video-assisted thoracoscopy (VATS). Failure to resolve the acute process satisfactorily can require later pleural stripping or decortication. Relatively large collections of fluid that form after appropriate antibiotic therapy has been initiated can usually be managed by serial thoracentesis, rather than by indwelling chest tube. The latter becomes necessary, however, if the patient unexpectedly remains toxic appearing or the fluid loculates.

**Intravascular Catheter-Related Infections**

Intravascular catheter-related infections remain one of the top three causes of nosocomial sepsis; however, in ICUs with organized prevention plans, the incidence can be reduced to a very low level. Despite better antibiotics, earlier recognition and improved understanding of the mechanisms of catheter-related infections, the case fatality rate for catheter-associated bacteremia remains significant.

**Mechanisms**

Three basic mechanisms can produce catheter-related infections (Fig. 26-4). (1) Most commonly, catheters are colonized at the skin-air interface, as bacteria migrate along their outer surfaces. Subcutaneous and eventual intravascular migration results in local infection or bacteremia if bacterial growth is uncontrolled by host defense or antibiotic therapy. (2) Catheters also can become colonized by exposure to circulating microorganisms introduced into the circulation at a distant site. As foreign objects, standard catheters routinely form a “fibrin sheath” or biofilm. This microenvironment is a stagnant, fertile environment for pathogen growth, helping sources
of bacteria or fungi far distant from the catheter to seed these indwelling lines. Although antiadhesive treatments that mimic the cellular glycocalyx and impregnated biocidal coatings such as silver salts and chlorhexidine are helpful, they encumber added cost and a universally effective prophylactic approach is not yet at hand. (3) Only rarely, catheter-related infections are due to the infusion of a contaminated intravenous fluid or drug. Although, in theory, such infusate contamination can occur with any drug, the problem has been reported most often with parenteral nutrition solutions and first-generation formulations of propofol, an intravenous sedative/anesthetic with a lipid vehicle.

**FIGURE 26-4.** Portals and pathways through which catheter-related infections can develop.

**Risk Factors**

Characteristics of patients at particular risk for catheter-related infection include diabetes mellitus, immunosuppressive therapy (especially neutropenia), immune deficiency diseases, skin diseases at the insertion site, and presence of sepsis at a distinct source. Physician and environmental factors increasing the risk of intravascular catheter infections include (1) catheter placement under emergency or nonsterile conditions, (2) insertion of multilumen catheters, (3) catheterization of a central vein, (4) prolonged catheterization at a single site, (5) placement by surgical cutdown, and (6) inexperience of the operator. Most catheter infections can be prevented by using sterile technique when inserting, dressing, changing, and reconnecting catheters and by minimizing the frequency of catheter access. Rigorous sterility during insertion is essential; apart from sterile
gloves, wide sterile barriers, surgical gowns, caps, and masks should be used for elective insertions. Chlorhexidine is superior to povidone-iodine solutions for skin preparation. Inexperience with catheter insertion increases infection risk. (It is not clear whether catheters become contaminated during insertion or if less experienced operators are prone to produce more tissue trauma during the insertion process.) Multilumen catheters or catheters entered repeatedly (even for antibiotic administration) seem to have a higher infection rate. Neither antibiotic ointment applied at the catheter entry site nor systemic antibiotics convincingly decrease the risk of bacteremia.

There is no clear evidence that determines the relative infective risk of internal jugular and subclavian sites when the duration of catheterization is controlled. Although the risk of pneumothorax is averted, the femoral approach limits leg movement, predisposes to deep venous thrombosis, and places the catheter in a region at risk for contamination by urine and stool, probably explaining the higher infection risk compared to sites above the waist. Central venous catheters are more likely to become infected than peripheral catheters (in part because of duration of catheterization). Peripherally inserted central catheters (PICC), which are usually inserted via a brachial vein, provide intermediate to long-term central access with a somewhat lower risk of infection. Pulmonary artery monitoring catheters and multilumen catheters (risk, 10% to 20%) are more likely to become infected than are single-lumen catheters (risk, approx. 5%). Interestingly, venous catheters are more likely to become infected than arterial catheters. Whether this differential risk relates to the shorter duration of arterial catheterization, the greater flow of blood in the artery, the shorter length of the arterial cannula, or the site of placement (usually in the radial artery) is unclear. Hypertonic fluids (peripheral total parenteral nutrition [TPN]) or highly caustic drugs (e.g., amphotericin, diazepam, phenytoin, erythromycin) may induce a chemical phlebitis, facilitating bacterial overgrowth.

To minimize the risk of infection, intravenous sites should be closely monitored and connecting tubing should be changed every 24 to 48 hours. Dressings that allow continual (sterile) observation of the wound puncture site are helpful for surveillance. Placing impregnated disc barriers around the catheter at its point of skin entry during insertion may help reduce the infective risk (Fig. 26-5). Blood withdrawal increases the risk of infection, as does the filling of tubing systems in advance of their use. Even minute quantities of blood or fat provide nutrients adequate to support the growth of most bacteria; therefore, changing tubing after infusing blood or lipids reduces infection risk. Continuous flush solutions and pressure-monitoring devices attached to arterial catheters pose special hazards. Reducing the number of catheter entries for blood sampling reduces infection risk. It is especially important to avoid contamination of pressure measuring catheters during calibration. Contamination of Swan-Ganz catheters may be reduced by minimizing the number of cardiac output determinations and by using sterile precautions during preparation and introduction of the injectate. Because of the escalating risk of infection, central venous and arterial catheters should be removed within 3 to 5 days of placement whenever possible. Obviously, there are situations in which all potential access sites have been exhausted or the risk of catheter reinsertion outweighs the risk of infection posed by leaving an existing catheter in place. Therefore, the need for and timing of catheter replacement must be individualized. There are no credible data to support a practice of routinely changing catheters over a flexible guidewire, and doing so in patients with established severe sepsis makes little sense unless all other sites and options for catheter insertion have been exhausted. Guidewire changes might make sense for patients in whom alternate sites for catheter insertion are unavailable or for those at unusually high risk for insertion of a catheter at a fresh site (e.g., coagulopathy, tenuous respiratory status, bilateral femoral vein thrombosis). When receiving a patient from another health care facility, as a general rule, it is reasonable to treat indwelling catheters as contaminated, regardless of their duration of insertion.
**Diagnosis**

Although redness, pain, and swelling around the insertion site strongly suggest infection, these signs are often absent in patients with catheter-related infection (Fig. 26-6). Local (soft tissue) catheter infections may be confirmed by Gram staining and culturing the catheter and by "milking the entry wound" to provide material for examination. Because intravascular infections usually produce recurrent and sometimes continuous low-level bacteremia, collecting several sets of cultures obtained over hours to days is sensible. A positive blood culture withdrawn through a potentially contaminated intravenous line does not necessarily establish a diagnosis of catheter sepsis; it is possible that the patient has systemic bacteremia from another source. That supposition is bolstered if the same organism is simultaneously recovered from a clean distant venipuncture site. However, if cultures from the catheter are positive but cultures from a peripheral stick negative, the catheter is suspect, especially if the catheter-obtained cultures grow rapidly. In patients with suspected "line" sepsis, the catheter, tubing, and fluids should be replaced with fresh components. Before catheter removal, the skin should be cleansed with chlorhexidine. The distal centimeter of the catheter tip should then be sent in a sterile container for culture and Gram stain. Semiquantitative culturing is performed by rolling the tip of the catheter across a culture plate. If more than 15 colonies of a single organism are isolated, infection is more likely than colonization. The catheter tip should not be placed into any solution for transport—doing so renders quantitative culturing impossible. Routine catheter changes over a guidewire are not rational in patients with sepsis or inflamed entry sites and are not necessary for asymptomatic patients.
Common Organisms
Although *S. aureus*, *S. epidermidis*, and *Candida* cause most catheter-related infections, enteric Gram-negative rods are recovered occasionally. Although rare, blood cultures growing *Enterobacter agglomerans*, *Pseudomonas cepacia*, *E. cloacae*, *Serratia marcescens*, *Citrobacter freundii*, or *Corynebacterium* species should suggest a contaminated intravenous solution.

Treatment
In almost all cases, contaminated catheters should be removed and cultured as outlined earlier (this includes PICC lines, temporary dialysis catheters, Portacath and Hickman devices). Blood cultures should be obtained from a site separate from the catheter insertion site. Considering the high incidence of MRSA in many ICUs, initial empiric antibiotic therapy for the patient with sepsis from a suspected intravenous line source should include vancomycin or other effective agent in doses adjusted for renal function. In units in which MRSA is rare, an antistaphylococcal penicillin is a reasonable initial choice in nonallergic patients. In either case, additional coverage for Gram-negative organisms should be included. Recovery of *Candida* from the catheter tip and blood culture usually requires parenteral caspofungin, fluconazole, or amphotericin B therapy. Vancomycin-resistant staphylococci may respond to linezolid, daptomycin, or quinupristin/dalfopristin.

Persistent Bacteremia
For patients with persistent bacteremia or fungemia, catheter infection and septic thrombophlebitis must be distinguished from bacterial endocarditis. The diagnosis of endocarditis usually obligates treatment with parenteral antibiotics for 4 to 6 weeks, whereas shorter courses of therapy are reasonable for line infections after the catheter is removed. The following factors all favor a diagnosis of endocarditis: (1) a new or changing (especially regurgitant) heart murmur, (2) valvular vegetations on echocardiogram, (3) physical stigmata of endocarditis, and (4) persistent bacteremia or fungemia after removal of the suspect catheter. Negative blood cultures should not dissuade the clinician from a diagnosis of endocarditis for patients with other signs: a small fraction of patients remain culture-negative off antibiotics, and an even larger group is difficult to be diagnosed because antibiotics suppress bacterial recovery. The transesophageal echocardiogram (TEE) has greatly enhanced the sensitivity of echocardiography to detect and stage heart valve lesions. Vegetations on the right-
sided valves do not firmly establish a diagnosis of bacterial endocarditis with universal certainty; central venous and pulmonary artery catheters crossing these valves can induce sterile vegetations.

It is difficult to make generalizations about endocarditis in critically ill patients because the condition may have been acquired in the community or may be a nosocomial problem, and these origins are associated with vastly different etiologic organisms, locations, and treatments. For patients with prosthetic valves who do not inject illicit substances, the left-sided heart valves (mitral and aortic) are those most often affected, and in such cases, the disease is either a subacute or acute problem usually caused by streptococci (40%), \textit{S. aureus} (20% to 30%), or \textit{Enterococcus} (10% to 20%). The viridans group of \textit{Streptococcus} is a common cause of the subacute form, whereas the acute variety is more commonly \textit{Staphylococcus}. For patients with prosthetic valves who inject intravenous drugs and for hospitalized patients subject to nosocomial bacteremia, the disease differs. There endocarditis is much more likely to be acute in nature and is most commonly caused by staphylococcal or streptococcal species. For these patient groups, Gram-negative rods and \textit{Candida} also are recovered with higher frequency. Infections developing while in an ICU and those associated with intravenous drug abuse are much more likely to occur on right-sided heart valves.

For patients with suspected endocarditis, several blood cultures should be obtained (preferably from different sites and before initiating antibiotic therapy). Recovery of organisms relates partially to the volume of blood cultured. A 12-lead electrocardiogram also should be obtained to look for evidence of conduction defects or arrhythmias, which suggest valve ring abscess. When a clinical diagnosis of endocarditis is confirmed, in most cases, an echocardiogram should be performed to look for vegetations, valve ring abscess, and rupture of valve leaflets. Each of these conditions is associated with increased morbidity (peripheral emboli), the need for surgical intervention, and mortality (possibly 50% higher than in the absence of these findings). The sensitivity of echocardiography has improved since the introduction of the TEE, which is capable of detecting small vegetations and those in positions previously not visible by surface echocardiography.

Intravascular foreign bodies (venous and arterial catheters, pacing wires) should be removed whenever possible. Empiric antibiotic therapy should be initiated against the most likely organisms based on history or clinical situation (Table 26-5). If valvular insufficiency, valve ring abscess, or fungal endocarditis is suspected or found, consultation with a cardiothoracic surgeon is indicated. Although most cases of subacute bacterial endocarditis on native valves can be managed successfully with antibiotics alone, Gram-negative or fungal infections, valvular incompetence, valve ring abscess, and disease on a prosthetic valve often require surgical intervention.

Persistent unexplained bacteremia (or, more rarely, fungemia), particularly when accompanied by pain, swelling, or redness at an intravenous site and recovery of a catheter-related organism, may signal supplicative thrombophlebitis, a condition often confused with endocarditis. A low threshold for surgical exploration should be maintained because this often subtle and highly lethal disease seldom will be cured unless the suppurated vessel is excised, despite the use of appropriate antibiotics.

<table>
<thead>
<tr>
<th>Table 26-5. Causes and Treatment of Endocarditis</th>
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<tbody>
<tr>
<td>Patient Characteristic</td>
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<tr>
<td>“Normal” host, community-acquired infection</td>
</tr>
</tbody>
</table>
Enterococcus patients or if resistant Staphylococcus or Enterococcus recovered (daptomycin second “backup” alternative)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Organisms</th>
<th>Therapy</th>
</tr>
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<tbody>
<tr>
<td>Prosthetic valve disease</td>
<td>Early postoperative: <em>S. epidermidis</em></td>
<td>Vancomycin plus aminoglycoside</td>
</tr>
<tr>
<td></td>
<td>Gram-negative rods</td>
<td>As above for normals</td>
</tr>
<tr>
<td></td>
<td>Diphtheroids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Late postoperative: (as above for normals)</td>
<td></td>
</tr>
<tr>
<td>Intravenous drug users</td>
<td><em>S. epidermidis</em></td>
<td>Vancomycin plus aminoglycoside</td>
</tr>
<tr>
<td></td>
<td><em>S. aureus</em> including MRSA, Gram-negative rods</td>
<td>Amphotericin B (consider adding flucytosine and surgery)</td>
</tr>
<tr>
<td></td>
<td><em>Candida</em></td>
<td></td>
</tr>
<tr>
<td>ICU acquired</td>
<td>Same organisms and therapy as for IV drug users</td>
<td></td>
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</table>

### Infectious Diarrhea

Diarrhea developing in the ICU is an extremely common problem. Its etiology often is multifactorial and rarely caused by bacteria associated with usual outpatient infectious diarrhea (e.g., *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia*). When diarrhea is infection related, a much more common condition is antibiotic associated or “pseudomembranous” colitis, more commonly known as “*C. difficile*” colitis. Although it is entirely reasonable to perform stool cultures and to examine the stool for inflammatory cells, ova, and parasites in patients recently admitted and predisposed to such pathogens, repeated culturing of patients with loose stools is cumbersome, expensive, and of very low yield.

### Pathophysiology

Pseudomembranous colitis is caused by toxins produced by *Clostridium difficile*. This hardy organism, often present in low numbers even in healthy persons, persists as the gut microbiome is narrowed by antibiotic pressure. As the organisms proliferate, clostridial toxin is released to directly attack colonic mucosa, in some cases producing the areas of mucosal damage that form the characteristic but inconsistently observed ulcerations known as “pseudomembranes.” Certain strains that have emerged in recent years (e.g., NAP1) are much more potent in generating toxins. Although classically described after
intravenous clindamycin therapy, *C. difficile* may overgrow the normal flora of patients receiving essentially any parenteral or oral antibiotic and those inoculated by the infective spores of other patients transmitted in health care environments. Spores from *C. difficile* can persist in the local environment for weeks to months. Alcohol-based disinfecting liquids do not eradicate these spores, mandating strict handwashing protocols and isolation measures to be taken by health care workers in order to prevent spread and limit outbreaks. Less commonly, colonic overgrowth in response to antibiotic therapy by other microorganisms (e.g., *Staphylococcus, Candida*) can give rise to a similar picture. Although years ago *C. difficile* colitis was an uncommon nuisance, now, mutations in the bacteria have made the disease potentially lethal.

**Signs and Symptoms**

*C. difficile* colitis typically presents with watery diarrhea on the fourth to ninth day of antibiotic therapy. Although usually guaiac positive, the stool is rarely bloody. However, bloody stools may result from one form of the disease localized to the hepatic flexure. Classically, crampy periumbilical and hypogastric pain and low-grade fever were common, and an “acute abdomen” was rare (see Chapter 37). Now, high fever, profound leukocytosis, and a presentation suggestive of bowel ischemia or infarction (elevated lactate) are often seen. As experience has accumulated, it has become clear that diarrhea may not always precede such toxic presentations.

**Diagnosis**

No routine laboratory test is diagnostic, but leukocytosis occurs in almost 80% of cases. As with other forms of inflammatory colitis, red blood cells and leukocytes usually are detectable in stool specimens. Diagnosis is confirmed by culturing *C. difficile* in profusion from the stool or by detecting bacterial toxin in fecal products. The toxin assay is readily available and less sensitive but more specific than stool culture. Some patients without *C. difficile* colitis have small numbers of the bacteria isolated from stool. If a diagnosis of staphylococcal or candidal antibiotic-associated diarrhea is being entertained, the microbiology laboratory should be notified when the stool specimen is submitted. Growth of *Staphylococcus* or *Candida* may not be reported as pathogenic unless near-pure cultures result or unless the laboratory is alerted in advance. The odor associated with *C. difficile* diarrhea is easily recognized by experienced health care personnel. Though infrequently performed, sigmoidoscopy often visualizes the colonic pseudomembrane that supports the diagnosis, but in a small fraction of patients (about 10%), only the right colon is involved. In such cases, a complete colonoscopy is required to find the characteristic lesions. In clinical practice, empirical therapy is usually initiated without endoscopy once the diagnosis is entertained.

**Treatment**

Systemic antibiotics should be minimized, and fluid and electrolyte support should be administered. Antidiarrheal agents should be avoided, because they may prolong colonic dwell time, thereby increasing the severity of the colitis. There is no evidence that giving lactobacilli to help restore the fecal flora is beneficial. Yet, restoration of a diverse and normal gut flora by “fecal transplantation” (bacteriotherapy) has been reported to succeed consistently in preventing recurrence. That procedure, seldom performed in critically ill patients, is usually attempted by colonoscopy, but success with delivery by nasoduodenal tube has also been reported. Because the toxin as well as the organism may be transmitted nosocomially, all
patients with this disease should be placed on contact isolation. Alcohol-based hand-disinfecting products commonly used in ICUs do kill the *C. difficile* bacteria, but as already noted do not kill the organism's spores. Therefore, it is important to decontaminate one's hands regularly with a prolonged soap and water wash. Aggressive room-disinfecting measures also must be taken for the room occupied by a recently infected patient.

Because it is effective, inexpensive, and not associated with the induction of bacterial resistance seen with vancomycin, metronidazole in doses of 500 mg *enterally* every 8 hours for 10 days is the therapy of choice. Vancomycin (125 to 250 mg *enterally* every 6 hours) for 10 days is appropriate in documented metronidazole failures. Intravenous metronidazole and vancomycin are less effective. Fidaxomicin, an antibiotic tightly targeted to *C. difficile*, appears currently to be an effective and attractive option, but experience with this agent is still accumulating. Bacitracin also has been used in doses of 25,000 units orally, four times daily, but is of uncertain benefit.

Treatment may fail because of reinfection, emergence of a vancomycin-resistant strain (rare), or bacterial transformation into a dormant spore phase. When therapy fails, relapses usually occur within 2 weeks of stopping treatment and will respond to a second longer course of metronidazole. It is in these patients that fecal transplantation is a highly appropriate consideration. It should be kept in mind that most episodes of recurrent or persistent diarrhea are not due to colitis associated with *C. difficile* but with one of the more benign noninfectious causes outlined earlier.

**Sinusitis**

Although radiographic evidence of sinusitis can be demonstrated in many supine patients with nasogastric tubes, nasal packing, or nasotracheal tubes, sinusitis often is overlooked as a source of occult fever in critically ill patients. Nosocomial sinusitis usually is polymicrobial with Gram-negative rods and staphylococci predominating. Cryptic fever may be the only clinical sign. Headache and facial pain may be impossible to detect in comatose or intubated patients. Nasal discharge usually is absent. Rarely, the paucity of overt clinical signs and inability of the patient to communicate may allow purulent sinusitis to advance to a life-threatening infection of the central nervous system. Its remote position and contiguity to vital structures render sphenoid sinusitis an unusually insidious process. Because bedside sinus radiographs are almost worthless (particularly for visualizing the sphenoid sinus), CT of the head with attention directed to the sinuses is the preferred method of diagnosis.

The best treatment for nosocomial sinusitis is prevention. Raising the head of the bed to a more physiological position may promote sinus drainage. Whenever possible, insertion of ostia-obstructing tubes into the nose should be avoided. For orally intubated patients, a standard orogastric tube can be placed easily for aspiration of the stomach, medication delivery, or feeding. Surprisingly, the incidence of acute sinus infection may be similar for nasotracheal and orotracheal intubations. Once infection is established, however, nasal tubes and catheters impede ostial drainage and should be extracted or exchanged for one that is orally inserted. Orogastic passage does not increase the level of patient discomfort and avoids the problems of ostial obstruction. When feeding tubes must be inserted through the nose, small-bore, flexible catheters are preferable. Most cases of sinusitis respond to tube removal, decongestants, and antibiotics. Specific bacteriologic diagnosis can be established by endoscopic sampling of fluid from the middle meatus, a procedure that is generally better tolerated than direct puncture of the sinus cavity. Because important pathogens include pseudomonas, acinetobacter, and staphylococci, empiric antibiotic selection should include an antistaphylococcal penicillin and an agent appropriate to those gram negatives. For community-acquired sinusitis, *H. influenzae* is a common etiologic organism that often requires therapy with a β-lactamase-resistant drug, such as a third-generation
cephalosporin. Adjunctive treatments may include decongestants, corticosteroids, and irrigation, but their efficacy in resolving a serious bacterial infection is not well established. Surgical intervention may be necessary for patients with suppurative complications of sinusitis (e.g., retro-orbital cellulitis, osteomyelitis, and brain abscess).

Meningitis

**Diagnosis**

Bacterial meningitis should be suspected in all patients with mental status changes, fever, and signs of meningeal irritation. Suspected bacterial meningitis is a genuine medical emergency that demands a precipitous workup and immediate broad-spectrum coverage. When neurologic symptoms begin, they often progress rapidly, but most patients with bacterial meningitis are ill for days beforehand. The presentation often is subtle in the ICU, where intubation and sedation limit communication. Fever, leukocytosis, and an otherwise unexplained change in mental status may be the only clues. When meningitis results from malignancy, tuberculosis, or fungal infection, the clinical picture is even subtler and more likely to include focal neurologic deficits and perhaps seizures. Although focal deficits are possible with uncomplicated meningitis, the presence of focal lesions should raise the possibility of an underlying or complicating brain abscess, subdural empyema, or epidural abscess. Bacterial meningitis may be mimicked by several noninfectious conditions, including: drug reactions to trimethoprim-sulfamethoxazole, ibuprofen, and OKT3; carcinomatous meningitis; subarachnoid hemorrhage; systemic lupus; and sarcoidosis.

**Organisms**

The microbiologic etiology varies with the site of acquisition (community vs. hospital) and patient age. The *Pneumococcus* remains the most common organism in community-acquired adult meningitis. Sinusitis, otitis, pneumonia, and endocarditis coexist frequently. *Neisseria meningitidis* is the second most frequent cause of sporadic meningitis. Nontypeable strains of *H. influenzae* represent the third. Although unusual in any setting, *Listeria* and enteric Gram-negative rods are especially rare when meningitis is acquired outside the hospital; however, in hospital-acquired meningitis, *S. aureus* or *S. epidermidis* and enteric Gram-negative rods are the leading etiologies, particularly following brain surgery.

**Diagnostic Techniques**

Examination and culture of spinal fluid offer the only conclusive method of diagnosing meningitis. In the absence of papilledema or focal neurologic deficits suggestive of a mass lesion, lumbar puncture (LP) may be performed safely without CT scanning. (Full-dose anticoagulation, uncontrolled coagulopathy, and significant thrombocytopenia constitute other relative contraindications to LP.) An LP may be impossible technically because of poor patient cooperation or lumbar disease. In such patients, LP under fluoroscopy or cisternal puncture may secure a specimen of spinal fluid.

Spinal fluid pleocytosis with a granulocytic predominance usually is documented in patients infected with bacteria. (Lymphocytic predominance suggests aseptic meningitis, herpes simplex encephalitis, Lyme disease, listeriosis, tuberculosis, partially treated bacterial meningitis, or other nonbacterial cause.) In the absence of a traumatic tap, large numbers of erythrocytes are rarely seen in the cerebrospinal fluid (CSF) of bacterial meningitis and suggest such alternatives as herpes encephalitis, head trauma, and subarachnoid hemorrhage. Eosinophils suggest a parasitic, cryptococcal, or coccidioidomycotic origin or a drug-related cause, such as those because of nonsteroidals, ciprofloxacin, vancomycin, and trimethoprim-sulfamethoxazole. With bacterial meningitis, the spinal fluid glucose level usually is less than 50% of the peripheral blood glucose value and CSF...
protein concentration often exceeds 100 mg/dL. Gram stain of spun spinal fluid demonstrates the organism in three of four cases of bacterial meningitis. It should be noted that seizures, tumors, trauma, and intracranial hemorrhage can mimic the CSF picture of meningitis. In particular, subarachnoid hemorrhage can present remarkably like bacterial meningitis. If the diagnosis of subarachnoid hemorrhage is not clear from head CT scan, it is useful to centrifuge a sample of freshly obtained spinal fluid and then examine the fluid for xanthochromia characteristic of subarachnoid hemorrhage.

Culture establishes a definitive diagnosis of meningitis. Although cultures of spinal fluid are positive in more than 90% of untreated cases of bacterial meningitis, the specimen may be rendered sterile by even a single dose of oral antibiotic. However, antibiotics rarely change the pattern of cells, glucose, or protein measurements in CSF for 12 to 24 hours. Leukocyte counts of 100/mm$^3$, protein levels higher than 100 mg/dL, and glucose values lower than 30 mg/dL are typical in bacterial meningitis. If spinal fluid cultures are sterile, antigen agglutination tests may reveal the etiology, especially when Pneumococcus or H. influenzae is causative. Because of wide cross-reactivity, these agglutination tests are least helpful in establishing or ruling out Neisseria infections. Blood cultures, positive in one third of patients with bacterial meningitis, should be obtained before instituting antibiotics. After the diagnosis of bacterial meningitis has been established, the clinician should be careful to exclude underlying pneumonia, abscess, or endocarditis before deciding on the dosing and duration of treatment. Viral, neoplastic, fungal, and tuberculous organisms all cause meningitis but generally present less urgently than acute bacterial meningitis.

**Treatment**

Although not nearly as contagious as widely feared, patients with suspected bacterial meningitis probably should be isolated until the organism is identified and 24 to 48 hours of antibiotic therapy have been administered. Even if spinal fluid cannot be obtained because of technical problems or concern over safety of the procedure, antibiotics should be administered as rapidly as feasible. If LP is contraindicated, unavoidably delayed, or technically impossible, empiric therapy should be initiated as efforts are undertaken to establish a delayed diagnosis by blood culture or antigen testing. Ideally, antibiotic therapy and its route of administration (intravenous, intrathecal) should be guided by Gram stain of centrifuged spinal fluid and modified in accordance with its culture. Although meningeal inflammation improves the penetration of most antibiotics into the CSF, certain drugs cross much more efficiently than others. For example, penicillin, chloramphenicol, and selected third-generation cephalosporins (e.g., ceftriaxone) cross the blood-brain barrier easily, whereas aminoglycosides and other cephalosporins may fail to achieve effective concentrations. Penicillin has long been the drug of choice for community-acquired meningitis when lancet-shaped Gram-positive cocci are present unequivocally. Yet, because the risk of penicillin-resistant Pneumococcus is significant, a good empirical regimen for initial coverage is a third-generation cephalosporin (or meropenem) and vancomycin. Small Gram-negative rods suggest H. influenzae, making a third-generation cephalosporin (e.g., cefotaxime, ceftriaxone) the drug of choice. If Gram stain suggests an enteric (large) Gram-negative rod or if there is evidence of a parameningeal focus (e.g., sinusitis, spinal osteomyelitis), an aminoglycoside should be added to a third-generation cephalosporin. (Aminoglycosides are never sufficient therapy alone, and even when clearly indicated for Gram-negative infections, consideration should be given to intrathecal administration.) For cases in which spinal fluid cannot be obtained or is nondiagnostic, a third-generation cephalosporin and vancomycin with or without ampicillin (if Listeria is considered) is the safest alternative. Because the spectrum of causative organisms in the hospitalized patient is so broad, initial therapy for nosocomial infections should include both vancomycin and a third-generation cephalosporin or meropenem. Acid-fast smears and cultures are negative in most patients with tuberculous meningitis. Therefore, empiric antituberculous therapy should be considered for
patients with subacute and chronic meningitis syndromes, especially if the CSF glucose concentration is low.

Although still somewhat controversial, preadministration or coadministration of dexamethasone with antibiotics may decrease the risk of long-term neurological deficits in patients with meningitis. This effect has been shown most convincingly for pneumococcal disease. If dexamethasone is given, typical doses are 10 mg IV every 6 hours for 2 to 4 days. Benefits of corticosteroid therapy are unproven if begun hours or days after initiating antimicrobial therapy.

Patients with acquired immunodeficiency syndrome (AIDS) certainly can acquire any form of bacterial meningitis, but a diagnosis of *Cryptococcus neoformans*, a common cause of meningitis in AIDS, must be pursued. The CSF inflammatory response in patients with untreated AIDS is often minimal; therefore, absence of an impressive pleocytosis should not dissuade one from the diagnosis of meningitis, especially if the glucose is low. Although an India ink examination of CSF reveals organisms in only 50% of cases, the CSF cryptococcal antigen is positive in almost 90%. Combining these two tests promptly identifies the disease in most patients. The remainder are diagnosed when cultures return positive. Because cryptococcal infection is so frequently a cause of meningitis in patients with AIDS, empiric amphotericin B probably is indicated unless CSF examination clearly indicates a bacterial cause. Tuberculous meningitis should also be considered when the patient infected with HIV presents with a syndrome of meningitis but has minimal CSF abnormalities. The higher frequency of brain abscess, toxoplasmosis, and central nervous system lymphoma in HIV-infected individuals necessitates a low threshold for head CT or MRI scanning, especially if focal defects are apparent on examination.

**Complications**

Four important complications of acute bacterial meningitis are (1) cerebral edema, (2) inappropriate antidiuretic hormone (ADH) syndrome, (3) obstructive hydrocephalus, and (4) seizures. Because one in three adults with meningitis experiences seizures, prophylactic anticonvulsant therapy is a rational adjunct. Signs of increased intracranial pressure (e.g., lethargy, papilledema, cranial nerve palsies, hemiparesis) should prompt emergent evaluation for cerebral edema or hydrocephalus by CT scanning. Unexplained hyponatremia (usually in conjunction with concentrated urine) should raise concern for syndrome of inappropriate antidiuretic hormone secretion (SIADH). Although rare, highvolume urine output with a rising serum sodium level should prompt consideration of diabetes insipidus caused by pituitary injury.

Craniotomy patients are at particular risk of meningitis caused by *Staphylococcus* and Gramnegative rods in the early postoperative period. Conversely, the *Pneumococcus* is responsible for more than 90% of late meningeal infections in patients with persistent posttraumatic CSF leakage. Septic cerebral embolism (e.g., from subacute bacterial endocarditis) and parameningeal infections (epidural abscess, brain abscess, sinusitis, and otitis media) are often confused with meningitis because they produce similar symptomatology and CSF pleocytosis. Paraspinal tenderness accompanied by radicular pain or weakness should be a clue to epidural abscess. *S. aureus* is the causative organism in more than one half of such cases.

Brain abscess most often is a polymicrobial infection caused by *Staphylococcus*, *Streptococcus*, and anaerobes. Abscess may develop by extension from the sinuses or ears or by hematogenous seeding (infected dialysis shunts, heart valves) or long-standing purulent lung disease (abscess, bronchiectasis). Brain abscess rarely is confused with uncomplicated bacterial meningitis because it usually presents with a less toxic picture and with focal neurologic signs. Unless otherwise guided by the dictates of culture and sensitivity results, penicillin together with chloramphenicol or metronidazole should comprise the treatment. In selected cases, a third-generation cephalosporin or antistaphylococcal agent may be indicated. Surgical
intervention generally is reserved for lesions that compress vital structures, those unresponsive to medical management,

and those for whom malignancy is a strong alternative possibility.

**FIGURE 26-7.** Layers of integument and associated infections.

### Soft Tissue Infections

A wide variety of skin and soft tissue infections can be encountered upon admission and after care is administered in the ICU (Fig. 26-7). These can be diagnostically obvious, superficial, and simple to treat or deceptively deep and life threatening. They are not always simple to distinguish from one another, so that high levels of suspicion and vigilance is advisable (Fig. 26-8). The frequency of soft tissue infections has increased significantly in recent decades predominantly because of an increase in infections caused by community-associated MRSA. *Staphylococcus aureus* is the most common pathogen isolated from complicated soft tissue infections, accounting for more than 40% of all cultured organisms. *Pseudomonas aeruginosa* is the second most frequently encountered isolate. *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, and enterococci comprise more than half of infections at surgical sites. The overall mortality rate for necrotizing soft tissue infections remains approximately 25%.

Many skin infections seen in the ICU are polymicrobial because they result from wounds incurred in surgical or accidental trauma, decubitus ulcers, and therapeutic or illicit vascular punctures or because they occur in patients with compromised defenses and vascular insufficiency (especially diabetes). Necrotizing infections of
the soft tissues are characterized by fulminant destruction of tissue, often (but not invariably) accompanied by impressive systemic toxicity and always associated with substantial risk of mortality. Microthrombosis, a tendency to spread along facial planes, and relatively little inflammatory cellular infiltrate characterize their pathology. Eponyms such as Fournier gangrene (pelvicoperineal necrotizing cellulitis), Ludwig angina (cervicofacial necrotizing fasciitis), and Lemierre syndrome (pharyngeal-jugular thrombophlebitis) have been applied to recognized variants of necrotizing cellulitis and necrotizing fasciitis.

Among the most impressive of these are gas-producing infections, which usually develop in the setting of tissue ischemia or gross contamination (Fig. 26-9). Risk factors for gas-forming infection include diabetes, penetrating foot lesions, peripheral vascular disease, and open trauma. Gas-producing infections may be classic gas gangrene with myonecrosis or a mixed organism (synergistic) necrotizing fasciitis. Both may spread with alarming speed. A mixture of aerobic and anaerobic organisms (Gram-positive cocci and Gram-negative rods) causes most gas-producing soft tissue infections. Classic clostridial gangrene occurs less commonly.

FIGURE 26-8. External appearances of common inflammatory skin conditions.

Aggressive soft tissue infections spread along fascial planes where blood supply is tenuous. Because observable cutaneous changes may be few, a high clinical suspicion is essential. Some of these life-threatening infections resemble a relatively uncomplicated cellulitis (Fig. 26-10). A number of general principles apply to the recognition of necrotizing infections: (1) soft tissue imaging, which is positive for gas, is more sensitive than physical examination; (2) CT and MRI improve detection of soft tissue gas; (3) identification of fluid and edema in tissue is neither sensitive nor specific for aggressive soft tissue infection; and (4) among important clinical
features are pain disproportionate to findings on physical examination, particularly if joint or muscle group use is compromised. Skin changes such as necrosis, cutaneous anesthesia, and formation of bullae may be helpful. Laboratory data are nonspecific and of limited diagnostic aid. Nonetheless, leukocytosis, hyponatremia, and elevated blood urea nitrogen (BUN) increase the likelihood of aggressive soft tissue infection. Where soft tissue infection is suspected, early surgical consultation is essential. Appropriate surgical treatment may include wide opening of tissue planes at the level of the fascia and excision of nonviable tissue. In some cases, effective debridement requires amputation of the infected extremity or distal portions thereof.

Necrotizing fasciitis is a pernicious infection that may easily elude detection until it is far advanced (Fig. 26-11). Diabetic patients usually have an obvious portal of entry in the foot or lower extremity but have relatively few signs of toxicity and relatively little local pain. Because such infections are usually due to gas-forming organisms, imaging of the lower extremity may be diagnostic. A different picture—“type 2” necrotizing fasciitis—is usually presented by nondiabetic patients who have high fever, often an inconspicuous portal of entry, and intense local pain out of proportion to the physical findings. Although infection may be polymicrobial, group A Streptococcus (or “GAS”) is the primary pathogen in most such cases. To achieve a successful outcome, a combined medical/surgical treatment approach must be executed rapidly. Cultures of blood should be obtained, in conjunction with biopsy or aspiration culture of the affected tissue. The primary indication for surgical intervention is severe pain in conjunction with a compatible clinical setting, toxic signs, and elevated creatine kinase. Physical examination may be seriously misleading (Fig. 26-11). Disease-consistent imaging studies may be supportive but are not required. If there is any suspicion that vaccination is not up to date, tetanus immunization and toxoid should be administered. Although the choice of antibiotics should be guided by Gram stain and culture, empiric regimens usually include an antistaphylococcal penicillin and clindamycin or metronidazole. Wider Gram-negative coverage is advisable in patients who have been recently exposed to antibiotics or who have been hospitalized for longer periods. Extensive debridement (or amputation) frequently is required for control of necrotizing fasciitis. As a general rule, dissection and excision of involved tissue is necessary down to the plane of uninvolved fascia (Fig. 26-12). Reexploration of the wound is usually indicated after 24 hours to ensure effective debridement of necrotic debris.
FIGURE 26-9. Extensive gas indicating deep tissue infection.
FIGURE 26-10. External appearance of skin or deep tissue infection.
A particularly virulent form of lower extremity tissue necrosis follows systemic or local infection with the bacteria *Vibrio vulnificus*. More commonly occurring in the immunocompromised patients and those with cirrhosis, the infection causes a rapidly progressive syndrome beginning with abdominal pain and blistering dermatitis. Within hours, microvascular thrombosis infarcts huge masses of tissue, sometimes whole limbs. Not surprising because of the ferocity of the illness, it is often fatal, despite prompt treatment with ceftriaxone and doxycycline—the recommended antibiotics.
FIGURE 26-12. The extent of necrotic infection (arrow) can only be determined by surgical exposure and excision down to plane of healthy tissue.

Most soft tissue infections at intravenous sites are the result of Streptococcus and Staphylococcus inoculated from the skin. Gram-negative rods may be causative in the colonized ICU patient. Removal of the catheter, application of warm compresses, and administration of analgesics and antibiotics usually resolve such infections rapidly. Treatment with a penicillinase-resistant penicillin usually will suffice. In less serious cases, oral therapy is acceptable. If methicillin-resistant staphylococci are likely, vancomycin represents appropriate initial therapy.

Toxigenic infections present a unique set of characteristics. “Toxic shock” syndrome, an uncommon but lethal disease often mediated by the Staphylococcus toxin TSST-1, was first reported in menstruating women using high-absorbency tampons. It is now recognized, however, that this syndrome occurs in many settings and can result from streptococci as well. Traumatic or postoperative wound infections may serve as the source for the toxin, even when the surgical wound itself appears uninfected. Toxic shock syndrome should be suspected in any patient with the triad of fever, erythematous (eventually exfoliative) rash, and shock. Therefore, toxic shock can be confused with Rocky Mountain spotted fever, Stevens-Johnson syndrome, leptospirosis, measles, or drug eruption. Because toxic shock syndrome is a toxin-mediated disease, local cultures are often positive for Staphylococcus, whereas blood cultures frequently remain negative. Therapy includes appropriate drainage (surgical drainage of wounds, removal of tampons), antistaphylococcal antibiotics (vancomycin is a good initial choice), and general supportive therapy with fluids, oxygen, and vasopressors.

Lethal infections that produce injurious toxins may also arise from the gastrointestinal tract, where some offending organisms are predisposed to proliferate in ischemic tissues. Patients having severe colitis in association with otherwise unexplained organ system compromise require urgent surgical consultation. This life-threatening syndrome is often but not invariably due to C. difficile. Patients experiencing colitis with progressive
failure of remote organs despite appropriate antibiotics and supportive treatment may require urgent total colectomy to control the systemic toxicity of this disease.

**Infection in the Immunocompromised Host**

**General Considerations**

Few clinical problems present a greater diagnostic challenge than fever in the immunocompromised host. Because such patients often have impaired function of multiple organ systems and undergo treatment with toxic chemotherapeutic agents, possible etiologies span a wide range of noninfectious and infectious agents. Multiple causes frequently coexist. Patients in this category have primary deficits of T-lymphocyte (cell-mediated), B-cell (antibody), or granulocyte (phagocytic) function. Knowledge of the type of immune deficit can help narrow the differential diagnosis. For example, T-cell disorders predispose patients to viruses and fungi, whereas B-cell disorders and granulocytopenia predispose patients to bacterial pathogens. Although loss of humoral immunity and T-cell functions predispose patients to infection, profound neutropenia (<1,000 granulocytes/mm$^3$) is the deficit that poses the greatest risk to life. Infections constitute a true medical emergency because in this setting, the speed with which appropriate therapy is begun largely determines outcome. Unfortunately, establishing a specific diagnosis often proves difficult. Such patients frequently fail to produce suppuration or other localizing signs of inflammation. Regardless of the type of immune defect or site of inflammation, the etiologic organism usually is one that normally resides as a commensal in the host. Although any site may be the target of infection, a few problems are characteristic in the neutropenic patient. These include mucosal infections (e.g., mucositis, gingivitis), “primary bacteremia,” soft tissue phlegmons (e.g., perirectal abscess), and atypical pulmonary infiltration.

**Pulmonary Infiltrates**

The problem of diagnosing pulmonary infiltrates in the immunocompromised patient is complex, and only a few salient features can be covered here. For febrile neutropenic patients, infection must always be the leading diagnostic consideration; however, progression of the primary neoplastic process, hemorrhage, pulmonary edema, graft versus host disease, radiation, and drug reaction are frequent causes of pulmonary infiltrates. Although virtually any organism can cause pulmonary infiltration in the compromised host, the clinician often can integrate knowledge of the immune defect, epidemiology, and clinical and laboratory data to narrow the spectrum of likely possibilities and formulate a logical approach. As a first consideration, the underlying disease may give some clue to the nature of the pathogen. For example, AIDS, a problem predominantly of helper T lymphocytes, predisposes a patient to *Pneumocystis*, mycobacteria, fungal, and cytomegalovirus (CMV) infections that a presumptive diagnosis often is suggested by the radiographic and clinical pictures alone. Nonetheless, the spectrum of possibilities remains wide until the cause is confirmed by biopsy or fluid examination. Epidemiologic factors also are important to consider. The duration of hospitalization before the development of pneumonitis influences the microbiology. For example, *Pseudomonas, Candida*, and *Aspergillus* infections are most likely to develop after many days in the hospital, whereas the likelihood of routine (community prevalent) pathogens wanes after the first few days of hospital confinement. Renal transplant recipients are unusually prone to CMV, herpes simplex, *Cryptococcus*, *Aspergillus*, and *P. carinii* infections during the period of maximal T-cell suppression, 1 to 6 months after operation. Neutropenic patients are highly susceptible to Gram-negative bacteria and fungal infections. (*Aspergillus* and *Mucor* become common infecting organisms if neutropenia is sustained longer than 3 weeks.) Concurrent infection with two or more organisms occurs commonly in patients with AIDS and in those undergoing renal or marrow transplantation. CMV, *Cryptococcus*, and *Nocardia* frequently are recovered in conjunction with other pathogens. (CMV and *Pneumocystis* are commonly associated.) Superinfections also occur frequently in immunosuppressed patients, particularly during sustained neutropenia and prolonged high-dose immunosuppressive therapy.
Certain clinical findings are especially noteworthy. *Legionella*, *Strongyloides*, and *Cryptosporidium* may cause diarrhea and pulmonary infiltration. Concurrent infiltration of the lungs and skin may result from *Pseudomonas*, *Aspergillus*, *Candida*, and varicella zoster. Hepatic and pulmonary diseases tend to coexist during infections with CMV, *Nocardia*, mycobacteria, and necrotizing bacteria (*Pseudomonas*, *Staphylococcus*).

**Evaluation and Therapeutic Approach to Pulmonary Infiltrates**

Unfortunately, these problems often defy easy diagnosis and a tissue biopsy frequently is needed. The pace of the disease may be very rapid, so that the objective is to cover broadly while attempting to establish a specific etiologic diagnosis expediently and safely. Two important questions must be answered to deal effectively with a life-threatening pulmonary process in a compromised host. First, considering that the process seems to be infectious and that the course cannot be determined easily, does a precise diagnosis need to be established or is empirical therapy sufficient? Second, if a precise diagnosis is required, what is the most efficacious technique for a fragile, critically ill patient? The answers to these questions are not straightforward and remain the subject of intense controversy. In general, the approach should vary with the severity of illness, the pace of advancement, the coagulation and ventilation status, the strength of ancillary information, and the experience of available personnel with specific invasive procedures. If diffuse infiltrates cannot be distinguished confidently from pulmonary edema despite CT imaging, a brief trial of diuresis may be prudent before proceeding to invasive diagnostic measures. Even when pneumonitis is certain, the astute clinician considers the potential contributions of hypoproteinemia and hydrostatic forces to the density of the infiltrates.

**Ancillary Data**

Both the characteristics of the chest radiograph at any single point in time and its rate of progression can provide helpful diagnostic clues. Localized infiltrates, either consolidated or nodular, are most consistent with bacterial or fungal infection, hemorrhage, or thromboembolic disease. Bilateral “interstitial” infiltrates, on the other hand, suggest volume overload, *Pneumocystis*, mycobacteria, or virus. However, serious lung infections may develop without impressive pulmonary infiltrates, particularly in neutropenic patients. A fulminant evolution suggests a bacterial process or a noninfectious etiology (fluid overload, embolism, ARDS). Conversely, a process requiring 1 to 2 weeks for full expression calls to mind mycobacterial, parasitic, or systemic fungal diseases. The severity of hypoxemia is another key observation. Explosive life-threatening depressions of blood oxygen tension are typical for bacterial, viral, and *Pneumocystis* infections but are less common with more indolent fungal and mycobacterial processes. Though exceptions may occasionally be encountered, bacterial pneumonia and sepsis reliably give rise to procalcitonin elevations. Body fluids from extrapulmonary sources can suggest a presumptive diagnosis for the chest infiltrate. Spinal fluid may demonstrate *Cryptococcus* but does not prove that the radiographic infiltrates are related. Nonetheless, in the appropriate setting, pleural and joint fluids should be tapped, examined, and cultured, and a stool specimen should be sent for parasite detection. Although blood cultures are unquestionably important, serologic testing rarely provides definitive information in an appropriate time frame.

**Pulmonary Secretions and Tissue**

Sputum is produced less frequently by the compromised host than by immunocompetent patients, especially when neutropenia is present. Nonetheless, when sputum can be obtained, its careful examination may reveal the responsible pathogen. In addition to the routine Gram stain, a direct fluorescent antibody test for *Legionella*, a phase contrast or cytologic preparation for *Blastomycosis*, an acid-fast stain for mycobacteria and *Nocardia*, and a silver stain for *Pneumocystis* and fungal elements are highly worthwhile. Concentrated sputum specimens may reveal *Strongyloides*. In patients with AIDS, such a profusion of *Pneumocystis* organisms is harbored that expectorated specimens often reveal them. Unfortunately, cultures of many pathogens require days to weeks for
growth, and the nearly universal practice of early, multiple broad-spectrum antibiotic use routinely obscures the diagnosis.

**THE NEED FOR BIOPSY**

If a specific diagnosis is not in hand after review of clinical data and laboratory results, the next step should be guided by the strength of clinical suspicion and the urgency of making the correct diagnosis. In most instances, bronchoscopy should be the first invasive procedure. Although coagulopathy and

the need for mechanical ventilation are moderate contraindications to forceps biopsy, lavage is virtually always feasible, and gentle, protected specimen brushings can be obtained safely when care is taken to administer platelets and/or deficient clotting factors beforehand. Bronchoscopic yield varies greatly with the specific disease process and with the timing and method of conducting this procedure. For example, when all specimen-gathering techniques (biopsy, brushings, and lavage) are used, a precise diagnosis can be established about 50% of the time. In special instances, such as patients with AIDS, the yield is considerably higher.

Open lung biopsy often is delayed because of its perceived morbidity and expense. In fact, open biopsy, a 20- to 40-minute procedure, is usually well tolerated and often helpful if conducted early in the course of the illness. It is the most reliable means of securing tissue for histologic diagnosis while establishing effective hemostasis in patients at high risk for bleeding. VATS is another approach of merit in patients with good hemostasis. The expense of open biopsy should be considered along with the high cost of empiric antibiotic therapy. Not only are multidrug combinations expensive, but also some of the commonly used agents carry substantial risk of toxicity for kidneys and bone marrow. Whatever the value of open lung biopsy may be when undertaken early in the course of disease, it is clearly less valuable after broad-spectrum antibiotics have been given for a prolonged period. In such instances, it is unusual for open biopsy to add sufficient new information to warrant its attendant drawbacks. Failure to define a specific etiology should not mandate continuation of empiric antibiotics indefinitely. Not only can antibiotic management be streamlined when a specific diagnosis has been made, but also rational reductions in therapy can be made in the patient improving on multiple drugs. Usually, this takes the form of sequentially removing the antibiotic least likely to benefit or most likely to cause toxicity from the combination every 1 to 2 days. The process of trimming antibiotic coverage often is delayed until patients are no longer granulocytopenic. Even while patients remain on multiple antibiotics, the clinician must remain alert to “superinfection” with a new or resistant organism. Furthermore, if a patient fails to improve with specific therapy directed against a known pathogen, a second organism commonly is present. For example, patients with AIDS and confirmed *Pneumocystis* pneumonia who fail to respond to trimethoprim-sulfamethoxazole often have coexistent CMV infection. When no specific diagnosis has been made and the clinician is forced to choose a regimen, it should be remembered that *Legionella* and *Pneumocystis* are among the most lethal and common pathogens. For the immunocompromised patient without a diagnosis, a third-generation cephalosporin and an aminoglycoside or quinolone, plus erythromycin or doxycycline and trimethoprim-sulfamethoxazole, are often chosen as initial therapy. When methicillin-resistant staphylococci are prevalent, vancomycin often is added or substituted. In centers in which fungi present a major problem, potent antifungals (e.g., amphotericin) are often begun very early in the course. The use of ultra-broad-spectrum antibiotics (such as the carbapenems) may help to greatly simplify initial coverage, but such drugs present their own set of problems in terms of expense and the induction of multiply resistant bacteria.

**Nonpulmonary Sites of Infection**

Neutropenia most frequently is an iatrogenic complication of antineoplastic chemotherapy. These same drugs profoundly impair host ability to maintain the integrity of tissues having rapid cellular turnover (e.g., bowel wall and the mucosae of gingiva and rectum). Therefore, it is not surprising that diffuse necrotizing colitis, anorectal
cellulitis, and typhlitis (a severe bacterial infection of the cecum mimicking appendicitis) occur relatively frequently. Violation of the normally intact integument by intravenous catheters, surgical incisions, or decubitus ulcers also opens a portal for bacterial entry. Therefore, for febrile neutropenic patients, the physical examination should routinely include catheter entry sites and the gingival and perirectal regions. Lack of tenderness with gentle palpation of the anal verge usually suffices to exclude this as a site of infection. All too often, no site is found for bacteremia or the sepsis syndrome.

**General Treatment Principles**

Survival of the neutropenic patient depends on early empiric therapy with more than one antibiotic effective against the infecting organism. The most common organisms include Gram-negative rods (particularly *Pseudomonas*), *Staphylococcus*, and fungi (e.g., *Aspergillus* and *Candida*). Patients with impaired cell-mediated immunity are more likely to be infected with *Pneumocystis* or *Candida*. When a site of infection is clearly definable, antibiotics should be chosen against the likely organisms. However, neutropenic patients frequently lack localizing signs of inflammation, and no likely source is found in most cases (even with careful examination). In such cases, cultures of blood, urine, sputum, and skin lesions should be obtained. Even though pyuria may be absent, microscopic examination of the urine may reveal large numbers of organisms. Broad-spectrum antibiotics, including extended-spectrum penicillin or third-generation cephalosporin plus an aminoglycoside, should be initiated. Vancomycin is warranted if the patient is allergic to penicillin, especially considering the prevalence of methicillin-resistant *Staphylococci*. In many centers, amphotericin or other antifungal agent is begun if the patient remains febrile for more than 72 hours after institution of broad-spectrum antibiotics.

**Postsplenectomy Infections**

Serious infections after splenectomy usually are due to encapsulated bacteria (e.g., pneumococci, *Salmonella*, *Haemophilus*). Loss of the spleen's phagocytic function allows unchecked bacterial proliferation. Similarly, loss of hepatic phagocytic function in patients with cirrhosis makes them subject to overwhelming infection. *Salmonella* and *Vibrio* species are two unusual pathogens seen in such patients. Therefore, in patients without a functional spleen (e.g., sickle cell disease), the prevention of infections and the early institution of antibiotics are essential.

**SUGGESTED READINGS**


Chapter 27
Sepsis and Septic Shock

• Key Points

1. Sepsis is defined as life-threatening organ dysfunction caused by dysregulated (as opposed to homeostatic) host response to infection. Septic shock is a subset of this condition, with circulatory and/or cellular/metabolic dysfunction and higher mortality risk.

2. Septic shock is a common condition that overall carries a 30% to 40% risk of death. Outcome is influenced strongly by the number and severity of organ system failures that occur.

3. Whereas disordered mental functioning and transient oliguria are almost universal, the lung and circulatory system are the two organ systems that overtly fail with highest frequency. Both manifest dysfunction early in the septic process. Circulatory failure usually reverses within days or proves fatal, whereas respiratory failure often requires 1 to 2 weeks of ventilatory support. Frank renal failure requiring dialysis is unusual. Cognitive function may remain abnormal for months after recovery.

4. Early fluid replacement and vasopressor therapy aimed at restoring adequate perfusion pressure are keystones of circulatory support. Glucocorticoids are a reasonable therapeutic option for patients with shock refractory to vasopressor support.

5. Infection source control, directed cultures, initial broad-spectrum coverage, and targeted antimicrobial therapy during deescalation phase are essential elements of treating septic shock.

TERMINOLOGY

Criteria for early recognition of sepsis and septic shock as well as guidelines for best therapeutic approach continue to undergo revision and refinement, perhaps because systemic infection occurs so commonly and with life-threatening consequences unless treated effectively. The term systemic inflammatory response syndrome (SIRS), a term in use for decades, is no longer thought well suited for practice by the most recent consensus of international experts (Fig. 27-1). Instead, “sepsis” is now defined as a life-threatening organ dysfunction caused by a dysregulated response to infection. “Septic shock” is the subset of sepsis with circulatory and/or cellular/metabolic dysfunction and higher risk of mortality (Fig. 27-2).

The shock state is identified by the need for a vasopressor (e.g., norepinephrine) to maintain a mean arterial pressure greater than 65 mm Hg in the absence of hypovolemia, accompanied by a lactate level greater than 2 mmol/L. Moreover, as more has been learned about the pathobiology of the syndromes associated with systemic infection, it was thought wise to dissociate the potentially homeostatic responses to infection (e.g., fever, leukocytosis, and tachycardia) from those that reflect the adverse organ response. Prominent among the latter are altered mental status, hypotension, and tachypnea. Whether the shock physiology of sepsis is driven primarily by impaired perfusion or by abnormalities of cellular energetics has not been settled. It is likely that causative primacy may depend not only on the individual but on the time point of observation.

An operational definition of sepsis is outlined in Table 27-1.

EPIDEMIOLOGY

The millions of cases of severe sepsis that occur each year across the world present huge medical, social, and economic problems. Severe systemic infections have no age or gender boundaries. With the exception of a spike
in frequency in the first year of life, septic shock has a low incidence throughout early adulthood and then an exponentially rising incidence, mortality rate, and cost after the age of 50. Although sepsis can develop in perfectly healthy persons, most patients have been hospitalized for several days before recognition of the condition.

Victims of trauma, immunosuppressed patients, and patients with chronic debilitating medical conditions (e.g., diabetes, chronic obstructive lung disease) or those undergoing complicated surgical procedures are most at risk.

**FIGURE 27-1. Formerly prevailing classification of systemic inflammatory states.** In this nosology, SIRS is defined by a specific pattern of vital sign abnormalities. Infection is the presence of a microbe within the host at a normally sterile site. When infection causes SIRS, the resulting syndrome is called sepsis (central overlap). If an organ failure results from sepsis, the syndrome is called severe sepsis.

Overall, approximately 30% of patients with septic shock die despite receiving “standard therapy” consisting of antimicrobial therapy and organ system support with fluids, vasoactive drugs, mechanical ventilation, dialysis, and nutrition. Such statistics motivate continuing efforts to recognize and optimally treat this high-risk patient group, as exemplified by the recurring *Surviving Sepsis* campaigns.

Elderly and hypothermic patients have a substantially worse prognosis than those without these factors; however, the best practical clinical predictor of outcome is the number of dysfunctional organ systems. Among the possible organ failures, circulatory failure (shock) has a disproportionately negative prognostic value. Morbidity and mortality from septic shock remain unacceptably high, and billions of dollars are spent caring for this desperately ill group of patients. Fortunately, survivors usually eventually regain premorbid levels of function in most organs; however, there is a growing awareness that a significant proportion of patients are left with long-lasting cognitive and neuromuscular impairments (see Chapter 18). The average survivor requires 7 to 14 days of intensive care support, with much of this time spent receiving mechanical ventilation. After intensive care unit (ICU) discharge, an additional 10- to 14-day hospital stay is typical. Thus, the hospital length of stay for survivors
averages 3 to 5 weeks. Massive hospital bills are often generated during the care of septic shock even when the course of treatment and recovery are relatively uncomplicated. After hospital discharge, long-term skilled inpatient care or challenging home care and rehabilitation are often required. Most survivors of septic shock are discharged on numerous medications, require office visits to physicians frequently during the year after discharge, and are readmitted one or more times for treatment of complications.

**FIGURE 27-2. Suggested revision of the classification scheme for septic conditions.**

**RELATIONSHIP OF INFECTION TO SEPSIS**

Recovery of a pure growth of a pathogen from a normally sterile site (e.g., blood or joint or cerebrospinal fluid [CSF]) diagnoses *infection*; however, most infected patients do not develop overt sepsis. This fact suggests that it is not infection per se that is etiologic but rather the combination of infection and host response that determines if an individual will develop organ dysfunction. Interestingly, a clear microbiologic explanation is absent in many patients, even though cultures grow some organism 60% to 80% of the time. Many of these “positive” cultures are obtained long after symptomatic sepsis or septic shock is established and represent insignificant colonization, contamination, or superinfection.

Common examples include growth of skin flora in one of several blood culture bottles, the recovery of a light growth of *Staphylococcus aureus* from sputum of a ventilated patient, or demonstration of a few colonies of *Candida albicans* in the urine of a patient with an indwelling urinary catheter. Perhaps the most convincing evidence of infection comes when several blood cultures obtained at the onset of the episode grow an identical pathogen consistent with the patient's clinical situation, for example, recovery of *Escherichia coli* in multiple blood cultures from an elderly man with bladder outlet obstruction and pyuria. Unfortunately, positive blood cultures are recovered in the minority of patients with advanced sepsis, and blood cultures are seldom positive if obtained after antimicrobial therapy is started. Despite historical teaching, there is little prognostic import of
having positive blood cultures, unless bacteremia cannot be eradicated. Inability to clear the circulation of organisms is often associated with an unresolved focus of infection (e.g., endocarditis or an infected foreign object) and portends a worse prognosis.

<table>
<thead>
<tr>
<th>Table 27-1. Sepsis Syndrome Criteria</th>
</tr>
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<tbody>
<tr>
<td><strong>I. Clinical evidence of infection</strong> (required)</td>
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<tr>
<td><strong>II. Major criteria</strong> (two of four required)</td>
</tr>
<tr>
<td>Fever or hypothermia (temperature &gt;100.4°F or &lt;96°F)</td>
</tr>
<tr>
<td>Tachypnea or high minute ventilation (respiratory rate &gt;20 or minute ventilation &gt;10 L)</td>
</tr>
<tr>
<td>Tachycardia (pulse &gt;90 in the absence of intrinsic heart disease or drug therapy inhibiting tachycardia)</td>
</tr>
<tr>
<td>Leukocytosis or leukopenia (WBC &gt;10,000/mm$^3$ or &lt;4,000/mm$^3$) or greater than 10% band forms on differential</td>
</tr>
<tr>
<td><strong>III. Acute impairment of organ system function</strong> (one required)</td>
</tr>
<tr>
<td>Altered mental status (reduction in Glasgow coma score &gt;2 points)</td>
</tr>
<tr>
<td>Hypotension (SBP &lt; 90 mm Hg or fall in BP &gt; 40 mm Hg refractory to fluid challenge)</td>
</tr>
<tr>
<td>Impaired gas exchange or acute respiratory distress syndrome (PaO$_2$/FiO$_2$ ratio &lt;300)</td>
</tr>
<tr>
<td>Metabolic acidosis/lactic acidosis</td>
</tr>
<tr>
<td>Oliguria or renal failure (urine output &lt;0.5 mL/kg/h)</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td>Coagulopathy (platelet count &lt;80,000/mm$^3$ or a 50% decline within 48 hours; INR &gt; 2.0; PTT &gt; 1.5 x control with elevated fibrin degradation products)</td>
</tr>
</tbody>
</table>

Remarkably, host responses that mimic sepsis are encountered in noninfected patients with severe pancreatitis, trauma, or burns, as these conditions produce similar biochemical changes, disordered physiology, clinical presentation, and outcome. This observation suggests that infection is not essential but rather that microbiologic stimulation acts merely as one disease trigger.

The lung is the most common site of infection leading to life-threatening sepsis, accounting for roughly half of all cases. Intra-abdominal infections (20% to 25%) and urinary tract infections (approx. 10%) are the next most common, with all other sites comprising the remaining 15% of infections.

**MICROBIOLOGY**

Bacteria, fungi, parasites, and viruses all can incite the sepsis syndrome. Because of the relatively high incidence of bacterial infections and relative ease in recovery of these organisms, bacteria are most commonly implicated. Limitations of diagnostic techniques make causative viruses difficult to identify. Historically, fungal infections were rarely etiologic in immunocompetent hosts, but with improved antibacterial agents and support techniques, increased numbers of immunocompetent patients now survive long enough to acquire a fungal infection. Distressingly, the frequency of fungal, particularly *Candida* infection, has risen dramatically over the past decades and now accounts for almost 10% of all sepsis-related episodes.
When a bacterial pathogen is identified, the frequency of gram-positive versus gram-negative bacteria is roughly 50:50. Discussions of the likelihood of gram-positive versus gram-negative infection are of limited value; the prevalence of organisms varies by location and over time, “cycling” under antibiotic pressure. Furthermore, knowing the frequency of each type of bacteria across a population is not particularly helpful in designing the initial treatment plan for an individual patient, except that such information can highlight unusual local resistance patterns.

For example, in some parts of the Southeastern United States, half of all *Pneumococcus* isolates are at least of intermediate resistance to penicillin. In addition, now in many ICUs, the single most common organism causing severe episodes of sepsis is a highly resistant nosocomial pathogen, typically methicillin-resistant *S. aureus* (MRSA) or vancomycin-resistant *Enterococcus* (VRE). Regardless, in most circumstances, critically ill patients require prompt empiric therapy for all reasonably likely organisms until culture data are available.

**PATHOPHYSIOLOGY**

The severity of sepsis is determined more by the specificity and ferocity of the host response than by the inciting organism. Ironically, the same inflammatory and coagulopathic mechanisms that are detrimental when intense, unrestrained, and undirected in the septic patient usually act as beneficial and effective defenses. Certainly, both confined inflammation and accelerated coagulation limit spread of local infection or injury. It is only when rogue, diffuse, unbridled inflammation, or coagulation occurs that they are counterproductive and organ damaging. Adverse host responses impair cardiovascular, neuronal, autonomic, hormonal, bioenergetic metabolic, and coagulation functions.

<table>
<thead>
<tr>
<th>Table 27-2. Common Mediators of Sepsis and Their Actions</th>
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</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td><strong>CELLULAR ELEMENTS</strong></td>
</tr>
<tr>
<td>Monocytes and macrophages</td>
</tr>
<tr>
<td>Neutrophils</td>
</tr>
<tr>
<td><strong>EICOSANOIDS</strong></td>
</tr>
<tr>
<td>Prostaglandins</td>
</tr>
<tr>
<td>Prostacyclin</td>
</tr>
<tr>
<td>Thromboxane</td>
</tr>
<tr>
<td>E-series prostaglandins</td>
</tr>
<tr>
<td>Leukotrienes</td>
</tr>
<tr>
<td><strong>CYTOKINES</strong></td>
</tr>
<tr>
<td>Tumor necrosis factor</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Interleukin-1  
Interleukin-6  
Interleukin-8

<table>
<thead>
<tr>
<th>OXIDANTS</th>
<th>Direct injury of lipids, nucleotides, and proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{H}_2\text{O}_2, \text{HOOCl}, \text{O}_2^- )</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PROTEASES</th>
<th>Destruction of vital cellular proteins, including antioxidants</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>CLOTTING PROTEINS</th>
<th>Microvascular thrombosis, leukocyte activation, inhibition of fibrinolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin</td>
<td></td>
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</table>

Historically, excessive inflammation was considered the major, if not sole, pathogenetic factor in severe sepsis. This paradigm envisioned a multistage inflammatory “cascade” in which an initial trigger caused production of a few “early” mediators, followed over hours by a larger number of secondary mediators (Table 27-2). Moreover, a linear progression from health to septic shock was envisioned, based primarily on the intensity of inflammation. It is now clear that inflammation, though extremely important and central to the sepsis syndrome, is but one of at least three important pathophysiologic pathways that includes enhanced coagulation and impaired thrombolysis.

The trigger for severe sepsis is often a protein, lipid, or carbohydrate toxin shed from a microbe but may be activated complement, a clotting cascade component, or dead host tissue. The most notorious inciting factor is endotoxin, the integral cell wall lipopolysaccharide component of gramnegative bacteria. However, it is far from being the only important toxin; staphylococcal toxic shock syndrome toxin (TSST-1) and group B streptococcal (GBS) toxin are other well-recognized triggers. The triggering compound usually is only transiently in the circulation and commonly escapes detection, even when sophisticated monitoring is performed. For example, less than one half of patients exhibiting septic shock ever have detectable endotoxin in plasma. This fact may help to explain the failure of antidotes developed to bind and neutralize circulating toxins. Development of sepsis does not require bacteremia or endovascular infection; toxic products may be released into the bloodstream from localized sites (e.g., abscesses) or directly from the colon (gut translocation), even when viable organisms do not circulate.

Tumor necrosis factor (TNF) and interleukin-1 (IL-1) have received the most attention as targets for modifying the septic response because they are potent, rapidly produced inflammatory compounds found in the tissues and circulation of many septic patients (Table 27-3). However, controversy exists regarding the significance of these circulating cytokines, and clinical trials designed to lessen levels of these compounds have not reduced mortality. That controversy notwithstanding, these cytokines are major stimulants for generation and release of other mediators, including IL-6, IL-8, enzymes, prostaglandins, leukotrienes, oxidant radicals, platelet-activating factor, and nitric oxide. Some activate coagulation (Fig. 27-3). Simultaneously with the dominant proinflammatory agents, anti-inflammatory mediators ramp up their activity.

Table 27-3. Experimental and Unverified Therapies for Sepsis
<table>
<thead>
<tr>
<th>Category</th>
<th>Proposed Action</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Nonspecific anti-inflammatory</td>
<td>Multiple failed human trials, possibly increases infection risk</td>
</tr>
<tr>
<td></td>
<td>Replacement of relative adrenal insufficiency</td>
<td>Inconsistent data from clinical trials</td>
</tr>
<tr>
<td>Naloxone</td>
<td>Opioid receptor antagonist</td>
<td>May transiently raise blood pressure, no effect on survival</td>
</tr>
<tr>
<td>Cyclooxygenase inhibitors</td>
<td>Reduce thromboxane and prostacyclin</td>
<td>Improved vital signs, no effect on survival, overall safe</td>
</tr>
<tr>
<td>Antiendotoxins</td>
<td>Inactivate gram-negative toxins</td>
<td>Several failed trials, possible harm suspected from one agent; trials ongoing</td>
</tr>
<tr>
<td>IL-1 receptor antagonist</td>
<td>Block IL-1 action</td>
<td>No improvement in physiology or survival</td>
</tr>
<tr>
<td>TNF antibodies</td>
<td>Inactivate TNF</td>
<td>No clear benefit</td>
</tr>
<tr>
<td>TNF receptor antagonists</td>
<td>Block TNF action</td>
<td>Dose-dependent increase in mortality</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>Prevent oxidant-mediated cellular injury</td>
<td>Trials ongoing</td>
</tr>
<tr>
<td>Toll-like receptor</td>
<td>Block inflammatory signal transduction</td>
<td>Positive phase II human trials, studies ongoing</td>
</tr>
<tr>
<td>antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue factor pathway</td>
<td>Inhibit tissue factor activation of coagulation</td>
<td>Studies ongoing</td>
</tr>
<tr>
<td>inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activated protein C</td>
<td>Antithrombotic, anti-inflammatory serine protease</td>
<td>No benefit in several trials. Possible harm</td>
</tr>
</tbody>
</table>

There is growing appreciation that abnormal coagulation is nearly universal in severe sepsis and that a complex interplay exists between clotting and inflammation. At the outset of the syndrome, tissue factor expressed by leukocytes and endothelium and cytokines lead to the production of thrombin by stimulating clotting factors V and VIII. Initially, the natural anticlotting systems (e.g., protein C, protein S, antithrombin) counteract the accelerated clotting. In this process, clotting proteins are consumed forming thrombi, and anticlotting proteins are depleted trying to inhibit clot formation. Because sepsis also impairs the host's ability to convert inactive anticlotting precursors to functioning proteins, clotting proceeds unopposed. As a second line of defense, endogenous fibrinolytic systems (e.g., plasminogen) are activated to dissolve the microvessel clogging thrombi, increasing plasma levels of clot degradation products.
Although routine clotting assays (e.g., prothrombin and activated partial thromboplastin times) may be near normal, abnormalities of clotting and anticlotting systems can be detected using more sensitive laboratory tests. The complex interrelationship among the three major pathways that mediate sepsis (inflammation, coagulation, and fibrinolysis) is still being elucidated by ongoing research. It is also clear, however, that counterregulating immunosuppressive activity begins from the very first stages of the proinflammatory response. One highly simplified schema depicting these interactions is illustrated in Figure 27-4.

FIGURE 27-3. Simplified representation of the early biochemical events in sepsis syndrome. In most cases, an inflammatory stimulus \textit{(upper left)} activates tissue-based and circulating mononuclear cells. The resulting production of tumor necrosis factor (TNF) and interleukin-1 (IL-1) can activate diverse nucleated cells. In response to TNF, other cells, especially neutrophils \textit{(upper right)}, release additional interleukins, more TNF, oxidant radicals, prostaglandins, leukotrienes, and proteases. TNF and IL-1 also activate adhesion molecules on neutrophils and vascular endothelium, resulting in cellular binding and vessel injury \textit{(bottom)}. Simultaneously, activation of tissue factor on white blood cells and endothelial cells results in accelerated clotting and inhibition of fibrinolysis.

**CLINICAL DIAGNOSIS**

Sepsis has many classic presentations: Group B Streptococcal sepsis in newborns, meningococcemia in young children, and staphylococcal toxic shock syndrome of adults. Unfortunately, such “classic presentations,” which include recovery of a specific organism, are exceptional. Sepsis is a clinical diagnosis, not one made by noting a single specific laboratory value or positive culture. Because a central tenet of improving the response to sepsis is early identification and intervention, detection of organ dysfunction at the earliest possible stage is a high priority. To this end, the quick qSOFA score, an
An abbreviated and user-friendly version of the well validated but more difficult to use sequential organ failure assessment (SOFA) score, has been developed, tested and advocated. Three clinically observable elements comprise qSOFA: (1) alteration of mental status (e.g., obtundation or confusion); (2) respiratory rate >22/min; and (3) systolic blood pressure less than 100 mm Hg. If two of these three elements are present, sepsis is likely or imminent. Although the qSOFA may not be infallible, more traditional clinical signs and measures are less specific or less reliable for organ dysfunction.

For example, although fever is present in more than 90% of diagnosed cases, it may reflect a normal homeostatic response or conversely, be minimal or absent in the elderly, in patients with chronic renal failure, or in those receiving steroids or other anti-inflammatory drugs. Indeed, hypothermia occurs in approximately 10% of cases of overt sepsis and is a particularly poor prognostic sign, with mortality rates in hypothermic patients approaching 80%. This high mortality rate is not due to the reduced temperature itself but rather the close linkage of hypothermia with chronic underlying disease, shock, gram-negative bacteremia, and/or a more ferocious host inflammatory response. Tachycardia, too, is an unreliable marker; it may be a sign of homeostatic behavior, rather than a sign associated with sepsis-defining organ dysfunction. Yet, unless patients have intrinsic cardiac conduction system disease or are receiving medications to prevent tachycardia (e.g., β-blockers, calcium channel blockers), tachycardia almost invariably accompanies sepsis. Oliguria (urine output <0.5 mL/kg/h for >2 hours), though a key clinical observation, may indicate an adaptive homeostatic response to hypovolemia, rather than organ injury by sepsis.
FIGURE 27-4. Interactive inflammation, coagulation, and immunosuppressive sectors of the septic response.

Respiratory rate, on the other hand, is a key vital sign, because newly developed tachypnea is an early harbinger of advancing sepsis. Although it is possible to have near-normal lung function with sepsis, the diagnosis should be questioned in patients without tachypnea or abnormalities of gas exchange; more than 90% of patients develop hypoxemia sufficient to require supplemental oxygen (usually a PaO$_2$/FiO$_2$ ratio below 300), and nearly 75% of life-threatening sepsis victims require noninvasive or invasive forms of mechanical ventilation. New abnormalities in circulating leukocyte (WBC) count (>10,000 cells/mm$^3$ or <4,000 cells/mm$^3$) occur frequently enough to be considered an important but highly nonspecific diagnostic criterion for sepsis. Among ICU patients, such leukocyte abnormalities are nearly universal.
In fatal cases of sepsis, it is the cumulative effects of organ system failures that cause patients to succumb. Therefore, understanding the usual onset, duration, and resolution of organ failure and methods of support assumes paramount importance. A clear relationship exists between the number of organ failures and mortality. Each new organ system failure adds roughly 15% to 20% to the baseline risk of death for all ICU residents (Fig. 27-5). Septic patients in the ICU typically average two to three failing organ systems at the time of diagnosis. The frequency of various organ failures noted at the time of diagnosis is shown in Figure 27-6. The most common constellation is the development of pulmonary dysfunction and shock. (Most patients developing shock also will be oliguric at least transiently.) Despite the multiplicity of causes, the pattern of organ failures in sepsis is remarkably similar among patients, with lung and circulatory failure developing rapidly (usually within 72 hours). Advanced central nervous system (CNS) dysfunction tends to develop later, although confusion is often the predominant manifestation of severe sepsis in the elderly. Oliguria is extremely common in the early stages of sepsis of whatever severity and does not always signal advancing kidney injury before resuscitation has been completed. Even though coagulation abnormalities exist in almost all victims of life-threatening sepsis, overt disseminated intravascular coagulation (DIC) occurs in only 10% to 15%, and its timing and its clinical recognition are unpredictable.
FIGURE 27-6. Prevalence of organ system failures at the time of diagnosis of severe sepsis. ARDS, acute respiratory distress syndrome; CNS, central nervous system.

Not only does the number of organ system failures correlate with outcome, but also the severity of each is important. For example, patients requiring high-dose vasopressors (>7 μg of norepinephrine) have mortality risks higher than those requiring lower vasopressor doses. Likewise, the mortality rates associated with higher creatinine levels resulting from sepsis associate with greater risk of death.

Specific Organ System Failures

Pulmonary

Pulmonary failure rarely is absent and usually is the first organ failure to be recognized. Perhaps respiratory failure is common because the lung is the only organ to receive the entire cardiac output, promptly exposing it to all the inflammatory and coagulation products released into the circulation. The lung's huge vascular surface area and delicate endothelial-epithelial capillary structure also play a role. Or, perhaps lung compromise is more easily detected, in that patients complain of dyspnea when they become hypoxemic or lung compliance declines and techniques for assessing pulmonary dysfunction (oximetry, arterial blood gases, and chest radiography) are applied promptly to ill-appearing patients.

Sepsis puts heavy demands on the respiratory system, requiring an increased minute ventilation to maintain oxygenation and compensate for metabolic (lactic) acidosis. Airflow resistance is increased, and lung compliance reduced, resulting in an overall increase in the work of breathing per liter of ventilation. These increased demands occur at a time when ventilatory power is compromised by diaphragmatic dysfunction and reduced respiratory muscle perfusion. The shortfall in muscle oxygen supply often leads to combined hypoxic and hypercapnic respiratory failure.

Most patients with severe sepsis require mechanical ventilation. The average duration of mechanical ventilation
for survivors is 7 to 10 days. Fortunately, fewer than 5% of patients require chronic ventilation, and fewer than 1 in 10 patients requires long-term oxygen therapy. Overall, almost half of patients develop acute respiratory distress syndrome (ARDS), defined as a PaO$_2$/FiO$_2$ ratio less than 200 with diffuse bilateral infiltrates resembling pulmonary edema on chest radiograph (not the result of left atrial hypertension). If ARDS develops, it happens rapidly, with most afflicted patients manifesting the syndrome within 48 hours of onset. Interestingly, there is only a rough correlation of PaO$_2$/FiO$_2$ ratio (P/F ratio) with mortality until the ratio falls below 100, at which time the P/F ratio becomes a powerful predictor of death. Paradoxically, the chest radiograph adds little prognostic information after the P/F ratio and lung compliance are considered. The good news about pulmonary dysfunction is that in essentially all survivors, the most severe manifestations of lung injury reverse within 30 days, although many months may be required for near-complete functional recovery.

### Circulatory Failure

Hypotension sufficient to meet criteria for shock (a mean arterial pressure <65 mm Hg, systolic blood pressure [BP] <90 mm Hg, or a fall in BP of more than 40 mm Hg unresponsive to fluid administration) is present in about one half of all septic patients at the time of diagnosis and develops in one half of the remainder within the first few days of illness. Understandably, of all organ failures, circulatory insufficiency typically has the shortest duration, averaging only 2 to 3 days. “Chronic” shock is rare: patients not reversing the shock state with aggressive life support usually die quickly. Surprisingly, blood pressure alone is a poor indicator of prognosis—pharmacologic elevation of blood pressure usually can be achieved; therefore, the blood pressure of treated patients with “shock” does not differ from that of patients without shock. Hence, clinicians can be lulled into a false sense of security if vasopressor requirements are not considered when evaluating blood pressure. Patients who require even low doses of a vasopressor for more than a few hours after adequate volume replacement have a mortality rate of approaching 40%, and the need for high doses of a vasoactive drug has been associated with nearly a 60% mortality rate. Although all experts agree that prompt and aggressive fluid administration is an essential first step in resuscitation, many advocate that pressors must not be delayed when the mean blood pressure does not quickly respond to the initial crystalloid bolus. Some critical beds lose their autoregulatory capability, leaving them vulnerable to low blood pressure, and sustained absence of adequate perfusion likely contributes to dysregulated bioenergetics.

For most hypotensive patients with severe sepsis, invasive monitoring will initially reveal a low central venous pressure (CVP) or pulmonary artery occlusion pressure (PAOP) and a normal or elevated cardiac output with a low systemic vascular resistance (SVR). In the current era of ready bedside availability of ultrasonography for the heart and great vessels, the vast majority of patients do not need placement of a pulmonary artery catheter. Intravascular pressures and volumes usually are low because of a combination of reduced fluid intake (anorexia), abnormal measurable losses (vomiting or diarrhea), greater insensible losses (sweating and tachypnea), and increased vascular permeability. Therefore, initial fluid requirements for resuscitation are substantial. It is common to infuse 4 to 6 L of crystalloid within the first 6 hours to raise the intravascular filling pressures into a range optimizing blood pressure and cardiac performance. Fluid deficits typically average 10 L or more in the first 24 hours. It is currently advised to administer greater than 30 mL/kg of intravenous crystalloid within the first 3 hours, with further rates guided by hemodynamic and circulatory measurements. Albumin is logical to add if large volumes of crystalloid have been administered.

Sepsis of high severity can also cause ventricular dilation and blunt myocardial contractility sufficiently to reduce cardiac output. Therefore, it is easy to see how septic shock with an elevated cardiac filling pressure and a low or low normal cardiac output may be mistakenly labeled “cardiogenic shock.” The key to differentiation when there is diagnostic uncertainty and an estimate of cardiac output is available is calculation of the SVR, which is
reduced in septic shock but elevated in cardiogenic shock. Unfortunately, the hemodynamic situation can be confusing when septic (vasodilatory) shock occurs in a patient with chronic congestive heart failure, the net result being a hypotensive patient with elevated intravascular filling pressures, a low cardiac output, and a near-normal SVR. Without echocardiographic supporting evidence, elevated skin temperature, delayed capillary refill time, and a reduced central venous oxygen saturation strongly suggest but do not define a major cardiac component. Failure to raise indicators of cardiac output when intravascular pressures are boosted is a poor prognostic sign that often reflects impaired cardiovascular reserve or sepsis-associated myocardial depression.

Renal Failure
Oliguria (urine output <0.5 mL/kg/h) is very common early in severe sepsis and tracks closely with shock. Up to 80% of patients develop at least transient oliguria, but it rarely persists beyond several days. Although the creatinine often rises modestly (range, 2 to 3 mg/dL), it is uncommon to develop frank renal failure. Only about 10% of patients with sepsis meet firm traditional criteria for dialysis or other forms of renal replacement therapy, and in more than 90% of survivors, dialytic support is brief (7 to 10 days). It is rare to develop permanent dialysis-dependent renal insufficiency from sepsis alone, unless baseline kidney function is significantly impaired; the elderly and patients with diabetes are at greatest risk for this complication. Interventions that can reduce the incidence of renal failure are to promptly treat hypovolemia and shock and to avoid use of nephrotoxic drugs (e.g., IV radiographic contrast, aminoglycosides) whenever possible. Agents like N-acetyl-cysteine, which are renal protective in other settings, have not yet been shown to be beneficial in sepsis.

Metabolic Acidosis
The pathogenesis of lactic acidosis in severe sepsis remains controversial. Clearly, in some patients with low oxygen delivery (DO$_2$) resulting from hypoxemia, anemia, or low cardiac output, impaired DO$_2$ alone can promote anaerobic metabolism. In other patients, lactic acidosis results primarily from maldistribution of cardiac output or from cellular malfunction, probably at the mitochondrial level. In a sense, the mitochondrial failure can be viewed as “organelle” failure much like other organ failures. Boosting DO$_2$ to prevent or reverse anaerobic metabolism and lactic acidosis has been extensively studied. It is clear that increasing DO$_2$ to some arbitrary supranormal value in established sepsis does not reverse anaerobic metabolism and may be harmful. By contrast, early vigorous resuscitation sufficient to correct insufficient oxygen delivery and normalize circulating lactate in the first few hours of the disease is likely beneficial. The finding that elevated lactate levels can occur in the absence of hypotension has been an important discovery because it can be used to identify a cohort of patients who may benefit from prompt, vigorous, protocolized resuscitative efforts. Yet, insufficient perfusion by measurable indicators such as cardiac output or lactate is clearly only one of the contributors to the shock state and cellular dysfunction. Restoring circulation adequacy may not fully address the mitochondrial dysfunction that arises from other noxious causes (Fig. 27-7). The point is that while assuring that inadequate oxygen delivery is certainly a rational objective, doing so cannot assure expedient recovery from mitochondrial and vital organ dysfunction. Nonetheless, clearance of lactate is a useful indication of resolving metabolic distress and shock reversal.
FIGURE 27-7. Mitochondrial dysfunction in sepsis. Excessive inflammation works via multiple pathways to impair mitochondrial function, cellular energy production, and physiologic performance of vital organs. RNS, reactive nitrogen species; ROS, reactive oxygen species.

Coagulation Disorders
The cause of dysregulated coagulation in patients with life-threatening sepsis is usually multifactorial. The two most important mechanisms are tissue factor expression from subendothelial cells and leukocytes and cytokine generation. The incidence of coagulation disorders varies depending on the defining criteria. For example, essentially all patients have reduced levels of specific clotting and anticlotting proteins and elevated clot degradation products. (Nearly, 100% of victims have elevated D-dimer levels, and 90% have reduced protein C levels.) Likewise, modest thrombocytopenia (platelet counts 75,000 to 100,000/mm$^3$), minimal reductions in fibrinogen, and minor prolongations of the prothrombin and partial thromboplastin times occur very commonly. However, full-blown DIC occurs in only 10% to 20%. When DIC does occur, it carries a poor prognosis, with mortality rates in excess of 50%.

Central Nervous System Failure
Minor declines in orientation and alertness are common and relatively early manifestations of sepsis, especially among the elderly. However, progressive worsening of the Glasgow coma score not otherwise explained by sedation portends a poor prognosis. As the mortality rate of severe sepsis has declined, it has become apparent that longterm cognitive problems afflict many survivors. Persistent difficulty with memory, concentration, and executive functioning can dramatically disrupt life quality post discharge.
FIGURE 27-8. Leaky gut syndrome. Luminal and circulating toxins may disrupt the healthy mucosal barrier, impairing nutrition and promoting systemic entry of noxious inflammatory and immunoregulatory products.

Gastrointestinal Failure

The gut is an early victim of the septic response, in that perfusion is diverted to more “essential” organs. Therefore, peristaltic function often temporarily ceases, producing ileus. For this reason, few physicians attempt full enteral nutrition until hemodynamic stability is achieved. Careful trophic feeding during this early period, however, is neither impractical nor unsafe. Because gut motility resumes shortly after BP and oxygenation are stabilized, enteral feeding can usually be ramped up 1 to 2 days after sepsis onset. The gut itself is believed to be a key “motor” of sepsis and associated shock. Once damaged by luminal or circulating toxins, the “leaky gut” may be a key source of inflammatory stimuli (Fig. 27-8).

In the distant past, significant upper GI bleeding resulting from gut ischemia occurred with substantial frequency (near 30%) unless pharmacologic prophylaxis was undertaken or early feeding begun. Now the combination of early resuscitation, earlier feeding, and nearly routine use of gastric acid suppression has all but eliminated life-threatening GI bleeding. Although controversial, the hypoperfusion of colonic mucosa also has been associated with leakage or “translocation” of bacteria and their toxins to the lymphatic and portal circulations. Unquestionably, the normally diverse gut microbiome is radically narrowed and altered by disease and antibiotic treatment. Attempts to minimize such potentially adverse changes with enteral probiotics are logical but unproven interventions. Profound hypotension, especially when prolonged, also can lead to hepatocellular injury—the so-called shock liver syndrome. Shock liver is characterized by significant increases in hepatic transaminases and bilirubin, whereas alkaline phosphatase tends to remain in the normal range or rise minimally. Sepsis-related
impairment of hepatic synthetic function is rare.

SEPSIS THERAPY

Primary directives in sepsis resuscitation are as follows: (1) detect and treat sepsis as early as possible; (2) correct hypovolemia; and (3) restore adequate perfusion pressure. Even though the foundation of sepsis treatment still remains infection source control, cultures, appropriate antibiotics, and prompt circulatory and ventilatory support, clinical trials have given us information about how best to perform these interventions. Among the most important developments in the care of the severe sepsis patient has been the recognition that outcomes can be optimized and money saved by applying a protocol-based approach delivered by highly trained caregivers.

Source Control

When the origin of the infective process is either known or strongly suspected, removal of the source (or containment of microbe proliferation when this is not possible) is a key therapeutic principle. Extraction of vascular catheters, drainage of obvious pus pockets, and even removal of implanted devices should receive careful consideration when no other potential source is likely. Up to one third of patients with sepsis admitted to the ICU require elimination or containment of the infection source to recover, typically for abdominal or soft tissue infections. Source control is accomplished in patients with soft tissue infections by aggressive surgical debridement, possibly including amputation. Patients with abdominal sources of sepsis frequently require drainage of infected fluid collections by transcutaneous catheter or surgery. Life-threatening intestinal infections and toxic colitis often need open operative procedures for resection, relief of obstruction, or establishment of effective drainage.

Antimicrobial Therapy

Drainage of closed-space infections and removal of infected foreign bodies or devitalized tissue are time tested and essential but not sufficient for cure of severe sepsis. Initially, a low threshold should apply for obtaining cultures of blood, urine, and sputum. Cultures of wound discharge, ascitic fluid, pleural fluid, and CSF should be performed as indicated by the history and examination. Collection of urine specimens for legionella antigen and pneumococcal antigen are sometimes helpful when initial blood cultures are unproductive. Though quite specific for the relevant subtypes of legionella and pneumococcus, sensitivity is less impressive, and these tests may remain positive for weeks after successful treatment. When negative, absence of infection is not assured, and when positive, they cannot be presumed as the culprit organism causing acute sepsis. Unlike procalcitonin, they have little place in monitoring efficacy of ongoing treatment.

The likelihood of making a culture diagnosis is maximized by obtaining specimens before antibiotics are initiated, but in some circumstances, this is not practical. For example, in a septic patient with suspected meningitis and a focal neurological defect, it is prudent to obtain a head CT before performing a lumbar puncture; however, it probably is not wise to delay antibiotic therapy while awaiting completion of these procedures. In this situation, it is better to begin empiric therapy, even if it may delay or obscure a specific bacteriologic diagnosis. In this scenario, blood cultures could be obtained before antibiotics are initiated and might yield a diagnosis.

Antimicrobial agents help kill the offending organism; they do not reverse the inflammatory—coagulopathic process. This fact notwithstanding, it makes sense to initiate antibiotics expeditiously. Until relatively recently, there had been little evidence to suggest that minutes or perhaps even hours in the time to administer antibiotics made a difference in outcomes. However, data now indicate that longer times to antibiotic administration are associated with higher mortality rates. For patients without shock, the urgency with which antibiotics must be given is less certain. For example, the national effort to rapidly administer antibiotics to patients with community-
acquired pneumonia has been associated with tiny improvements in survival.

Selection of an appropriate antibiotic early in the disease course is clearly important, however; patients with sepsis who do not have the offending organisms properly treated in timely fashion die more frequently than those given adequate coverage. This observation should be interpreted cautiously, however. The reason for “inadequate” antibiotic coverage is often that patients are infected with highly resistant or unusual organisms as the result of chronic illness, long hospital stays, previous antibiotic exposures, or immunocompromised states. Failure to respond to seemingly appropriate antimicrobial therapy may be the result of an undrained closed-space infection (e.g., empyema, intra-abdominal abscess), presence of a resistant organism, insufficient drug levels, or most commonly simply insufficient time for response after starting therapy.

Antibiotics should be chosen based on individual patient factors (e.g., immunosuppression, allergies, and underlying chronic illnesses), the presumptive site of infection, pattern of local antibiotic resistance, and examination of body fluids/specimens. For the patient with profound sepsis, initial broad-spectrum antibiotic coverage with at least two antibiotics of different antimicrobial classes aimed at the most likely pathogens is indicated until culture and sensitivity data return. Unfortunately, changes in resistance patterns induced by injudicious past use of antibiotics now frequently necessitate three or sometimes even four antibiotics to provide empiric coverage. The stark reality is that we are unable to anticipate or provide empiric therapy for all possible organisms.

In the absence of diagnostic clinical specimens, the presumed site of infection probably is the most helpful basis on which to select antibiotics. An in-depth discussion of appropriate empiric coverage based on the presumptive site of infection is provided in Chapter 26. Because lung and abdominal infections are most common among patients with sepsis, therapy with a third-generation cephalosporin or extended-spectrum penicillin and a quinolone or aminoglycoside is a reasonable first combination when no clear site of infection can be found. In many cases, vancomycin also should be added to primary coverage if penicillin-resistant pneumococci or methicillin-resistant staphylococci are prevalent regional pathogens. When an “atypical” organism is suspected as the cause of pneumonia, a quinolone, doxycycline, or macrolide should be included in coverage. Antifungal agents may be appropriate to add in specific patients at unusually high risk for mycological sepsis. Because most antibiotics are concentrated in urine, bacterial urinary tract infections are usually easily treated with almost any antibiotic, unless drainage is obstructed. In suspected meningitis, initial therapy should always include at least vancomycin and a third-generation cephalosporin such as ceftriaxone. Finally, high suspicion of an anaerobic infection should usually prompt addition of metronidazole or clindamycin. Within reason, it is best to begin therapy in the critically ill patients with “too broad” a spectrum and then narrow coverage as more clinical response is evaluated and/or culture data become available. With that caveat, antibiotic coverage should be reassessed on a daily basis, and unnecessary drugs should be stopped promptly (antibiotic “deescalation”). Combination therapy is neither prudent nor necessary once the offending organism(s) is identified and its sensitivity antibiogram is determined. Likewise, combination therapy is neither needed nor advised for the routine treatment of neutropenic sepsis and bacteremia. The duration of treatment is generally 7 to 10 days, and a falling procalcitonin level encourages cessation after day 7. Contrary to popular belief, antibiotic therapy is not benign. Use of excessive or unnecessary antibiotics is costly, risks allergic reactions and toxicity, raises the likelihood of later superinfection, distorts and narrows the gut and body surface microbiomes, and, perhaps most importantly, breeds the emergence of highly resistant bacteria that can harm future patients. Obviously, even when appropriate initial antibiotic choices are made, the doses must be adjusted to ever-changing levels of renal and hepatic function.

Respiratory Support
Because of the high frequency of hypoxemic respiratory failure, airway intubation, supplemental oxygen, and mechanical ventilation usually are necessary. The specifics of airway control and the principles and problems of mechanical ventilation are presented in detail in Chapters 6, 7, 8, 9 and 10; however, some unique features of sepsis-induced lung injury deserve mention. More than 75% of sepsis victims eventually develop respiratory failure of sufficient severity to require invasive mechanical ventilation, and nearly all require supplemental oxygen. Therefore, for septic patients with marked tachypnea (respiratory rate higher than 30), and marginal oxygenation, it is prudent to plan for elective intubation. It is counterproductive to pretend that rapidly evolving tachypnea and desaturation will resolve spontaneously. Doing so often results in emergent intubation of an apneic patient, and only rarely can patients sustain indefinitely a respiratory rate greater than 30 breaths/min. Similarly, sepsis or sedative-related obtundation, the prolonged duration of respiratory failure, and high levels of ventilation that expose spontaneously breathing patients to risk of excessive transpulmonary driving pressures often make inadvisable or portend eventual failure of noninvasive ventilation strategies.

There is no clear best mode of ventilation for all septic patients; however, it makes sense to provide nearly full support, in many cases only achieved by temporary use of deep sedation and neuromuscular blocking agents. Full support, especially for patients in shock, permits redistribution of cardiac output from the respiratory muscles to other parts of the body. The cardiac output sparing effect of ventilatory support can be substantial, in many cases amounting to an effective 20% boost in systemic oxygen delivery.

Often, the drive to breathe is so high that sedation is needed to match the respiratory efforts of man and machine. To maximize patient matching and comfort, special consideration should be given to altering the gas flow delivery pattern and flow rate.

For patients with sepsis-induced acute lung injury, initial tidal volume selection should approximate that of a normal spontaneous breath (5 to 7 mL/kg of ideal body weight), provided the resulting plateau pressure remains below 30 cm H\textsubscript{2}O and driving pressure does not exceed 15 cm H\textsubscript{2}O. Higher plateau pressures mandate additional tidal volume reductions. Limiting plateau and driving pressures reduce alveolar stretch and hence the risk of classical barotrauma and "biotrauma," the name given to the local and systemic inflammatory response generated by imprudent ventilation. When flow rate adjustments and sedation fail to relieve dyspnea or control dyssynchrony, strong consideration should be given to paralysis and permissive hypercapnia so as to limit the minute ventilation, strain, and driving power that risk ventilator-induced lung tissue injury (VILI, see Chapters 8 and 24).

Supplemental oxygen should be administered to maintain an acceptable arterial saturation (in most cases, S\textsubscript{a}O\textsubscript{2} higher than 88% but <97%). Although high FiO\textsubscript{2} is a co-contributor to lung injury and may even cause adverse microvascular constriction in certain critical tissue beds (e.g., coronary), in the earliest stage of life-threatening sepsis the real and immediate risk of hypoxemia should not be traded for the perceived hazards of oxygen toxicity. Lower saturation limits are acceptable for young, otherwise healthy patients, whereas higher targets may be appropriate for patients with myocardial ischemia or recent stroke. Uncertainties surround the potential for oxygen toxicity; however, common practice is to attempt to reduce FiO\textsubscript{2} to a level of 0.6 or less, provided arterial O\textsubscript{2} saturation remains acceptable. If higher FiO\textsubscript{2} is required, sequential upward titration of positive end-expiratory pressure (PEEP) usually is undertaken. On the basis of current evidence, the "best PEEP" for these patients is often the lowest PEEP that provides acceptable O\textsubscript{2} delivery with an FiO\textsubscript{2} at or below 0.6 with acceptable airway plateau and driving pressures. Some minimal level of PEEP (5 to 10 cm H\textsubscript{2}O) is probably beneficial for all mechanically ventilated patients to raise functional residual capacity and minimize injury induced by the repeated phasic opening and closing of alveoli. The higher minimum for PEEP is particularly applicable to patients managed at head of bed angles less than 45 degrees and those with obesity or other reasons for increased
intra-abdominal pressure. Randomized trials in acute lung injury have failed to show routine benefit from higher levels of PEEP (12 to 15 cm H$_2$O) compared to lesser amounts, but the very earliest recruitable stage of ARDS—frequently occurring in sepsis—may be one exception (see Chapters 8 and 9). Paralytics and prone positioning are often indicated when moderate to high levels of PEEP fail. Despite the intellectual emotion that sometimes surround the selection of PEEP and FiO$_2$ and use of other measures to improve oxygenation, most patients with sepsis-induced ARDS end up receiving an FiO$_2$ between 40% and 60% and PEEP of 8 to 10 cm H$_2$O pressure and require no extraordinary interventions.

**Resuscitation and Post-resuscitation Fluid Management**

The latest international consensus of sepsis experts recommends a protocol for resuscitation that initially targets a CVP of 8 to 12 mm Hg, a mean arterial pressure greater than 65 (but not >80 mm Hg), urine output greater than 0.5 mL/kg/h in those without preexisting renal failure, and a central venous oxygen saturation greater than 70%. Contrary to long-standing belief that aggressive fluid administration increases the likelihood of need for positive pressure ventilation, data from hospitals undertaking a protocolized approach to the resuscitation of patients with septic shock suggest that prompt fluid resuscitation reduces that requirement. Another important development in the care of the patient with sepsis-induced lung injury has to do with fluid management after shock has resolved. Minimizing nonessential fluid intake and using diuretics to target a CVP less than 4 mm Hg appears to shorten the period of mechanical ventilation by 2 to 3 days, without increasing the incidence of recurrent shock or renal failure.

**Cardiovascular Support**

Septic shock is often recognized in part by mean arterial pressure less than 65 mm Hg, systolic BP lower than 90 mm Hg or a decrease in normal systolic BP of more than 40 mm Hg unresponsive to fluid administration. Supportive data include reduced central venous hemoglobin saturations or elevated arterial lactate concentrations. At the onset of the syndrome, most patients with sepsis-induced shock have substantial volume depletion with variable degrees of systemic vascular dilation and myocardial dysfunction. Ventricular filling pressures are usually low because patients have been deprived of oral intake and have increased fluid losses (from sweating, panting, vomiting, or diarrhea). Moreover, they have dilated capacitance vessels and increased endothelial permeability. The average septic patient requires 4 to 6 L of crystalloid fluid replacement or a comparable volumeexpanding amount of colloid within the first 6 hours to optimize ventricular performance and perhaps double that amount of fluid in the first 24 hours. Pressors may substantially reduce the fluid volume needed.

There is no proven difference in efficacy of crystalloid and albumin, although recent trial and metaanalyses suggest that certain colloids (such as starch) should not be used and that crystalloid may be the better choice. Neither colloid nor crystalloid remains confined entirely to the vascular compartment in sepsis. And although less colloid is generally required for volume expansion, this potential benefit is achieved at substantial cost—synthetic colloids risk allergic reactions and may contribute to renal dysfunction and high economic price. Albumin is currently the preferred type of colloid and may be prudent to add after many liters of crystalloid have been infused. Because hemodilution accompanies resuscitation with colloid or crystalloid, packed red blood cells are often used to maintain hemoglobin concentrations in an acceptable range, although the appropriate target for hemoglobin concentration likely varies among patients depending on presepsis baseline and cardiac reserve, a transfusion threshold that exceeds 7 to 8 g/dL has been advocated as a general guideline value.

As discussed in Chapter 13, massive saline infusion provides a chloride load that may contribute to acidosis and stress the excretory capabilities of the dysfunctional kidney. Primarily for these reasons, many intensive care
specialists prefer to administer some portion of the crystalloid as balanced salt solutions (acetate, Ringer, Hartmann) so as to avoid the chloride load. Although this practice seems logical, any administered lactate may confound interpretation of monitored serum lactate levels to some extent, especially in patients with ongoing lactic acidosis and/or liver dysfunction.

Despite informative clinical trials highlighting the benefits of prompt and generous fluid administration, there remains controversy with regard to the optimal fluid volume to be infused, the rate of administration, and the method of monitoring the adequacy of therapy. Each physician seems to have a different level of comfort with regard to the amount of fluid infused before instituting invasive monitoring or starting a vasoactive drug. The widely proffered recommendation to “replace circulating volume” before instituting a vasoactive drug is sensible but inexact, because there are no certain guidelines for intravascular filling pressure goals or even which pressure to target (CVP or PAOP). One resuscitation strategy shown to reduce mortality in septic shock used a target CVP of 8 to 12 mm Hg. Adding a vasopressor is reasonable if mean systemic blood pressure remains less than 65 mm Hg and CVP exceeds that lower threshold.

Treatment strategies range from giving fluid boluses guided only by the clinical exam (i.e., blood pressure, pulse rate, skin color and temperature, and urine output) to the addition of CVP measurement, all the way to pulmonary artery catheterization with mixed venous oxygen saturation monitoring. Although the best measure of left ventricular filling is probably the PAOP, adequacy of left ventricular preload remains uncertain even when PAOP and esophageal (pleural) pressure known because of the difficulty of estimating ventricular compliance. Determining the dimensions of the ventricles by ultrasound is a helpful if imprecise adjunct. Functional monitoring accomplished by measuring hemodynamics (CVP or PAOP) in response to rapid fluid challenges (such as the leg lift) holds the logical appeal. When an administered fluid challenge is used, it is important to use a quickly delivered bolus of sufficient volume to cause a detectable change. A commonly selected “bolus” size, 500 mL, has been shown to produce little measurable change in blood pressure, intravascular filling pressures, or cardiac output. Thus, it makes sense to use larger fluid challenges (≥15 mL/kg) unless there is a strong suspicion that cardiac performance is profoundly impaired. Likewise, it is logical to administer the bolus as rapidly as possible to maximize the chance of achieving and detecting a positive hemodynamic effect.

A treatment strategy of early “goal-directed” therapy (EGDT) was reported in the Rivers trial to dramatically improve survival of patients with profound sepsis. This strategy used fluids to achieve a target CVP (8 to 12 mm Hg), followed by vasopressors to attain a target mean arterial pressure of 65 to 95 mm Hg. Then, patients with persistently low superior vena cava oxygen saturations (<70%) were given red blood cells if anemic or dobutamine if not anemic to reach a specific superior vena caval saturation target. In contrast to previous potentially harmful strategies targeting an arbitrary level of oxygen delivery in established sepsis, this strategy focused on early (first 6 hours) correction of circulatory abnormalities. This strategy was historically important in calling attention to the importance of early, aggressive intervention, and protocolized correction of hypovolemia. Since its introduction, however, the EGDT concept has been tested and refined for different settings. In evaluating patients with less profound sepsis and higher vena caval O₂ saturations, two large trials found little advantage to further aggressive administration of fluids and vasopressors toward a goal once the initial stage of hypovolemia had been addressed and broad-spectrum antibiotics had been given.

Another influential trial showed no significant benefit to targeting mean arterial pressures greater than 65 mm Hg (or 75 mm Hg in those with previously known hypertension). Even if the specific original protocol and targets of the EGDT may not be appropriate for all septic patients, the need for expedient and vigilant attention to the key therapeutic components of early correction of hypovolemia and restoration of a minimally adequate mean arterial pressure should not be questioned on the strength of current evidence.

A detailed discussion of vasopressor therapy is provided in Chapter 3; however, a few points deserve
highlighting. Vasopressors are of limited effectiveness in severely volume-depleted patients and can be detrimental if given in doses that compromise tissue perfusion. In septic shock, hypotension is predominately the result of reduced SVR, with a lesser contribution from impaired cardiac contractility. Thus, drugs with both β-adrenergic (cardiac stimulatory) and α-adrenergic (vasoconstrictive) properties make sense. As a practical matter, in the fluid unresponsive patient, physicians usually initiate circulatory support with dopamine (5 μg/kg/min) or norepinephrine (2 μg/min) and then titrate the infusion upward as needed. Historically, dopamine had been favored because of its alleged (but insignificant) “renal protective” and contractility stimulating effects; however for sepsis, dopamine has been displaced by norepinephrine (+/- dobutamine) because clinical trials and practical experience have made clear that dopamine does not protect the kidney, is less effective at raising blood pressure until dosing enters the upper range, and is more likely to cause tachycardia than norepinephrine. Vasopressin may be an effective addition once norepinephrine dosing approaches its uppermost dose. Recognition that many patients with septic shock have low plasma vasopressin levels and administration of low doses of vasopressin (0.01 to 0.04 U/min) raises blood pressure has led many clinicians to use vasopressin routinely or in patients with hypotension resistant to moderate doses of catecholamines. Results of a large randomized trial of vasopressin in septic shock indicate that low doses of vasopressin are safe and effective at raising blood pressure, but do not routinely afford significant benefits with regard to survival compared to catecholamines alone. A pure α-adrenergic agent (e.g., Neo-Synephrine) may also be considered in this setting of norepinephrine refractory vasoplegia. Although empiric, some clinicians choose epinephrine or add dobutamine to an existing vasopressor regimen if cardiac index appears inappropriately low (<2.5 L/min/m²).

One widely held misconception is that the use of potent vasoconstrictive agents (e.g., norepinephrine, phenylephrine, vasopressin) promotes or at least portends a poor outcome. To the contrary, sometimes, it is only after norepinephrine is begun that SVR increases sufficiently to raise the mean arterial pressure and restore organ perfusion. In certain settings (e.g., cor pulmonale), failure to raise systemic blood pressure will deprive the heart of the coronary perfusion gradient it needs to pump effectively.

Physicians and nurses often become anxious when the required dose of any vasoactive drug is higher than that used in their past experience. However, it should be kept in mind that individual patient responsiveness to vasopressors can differ widely (perhaps a log variation in dose). Therefore, there are no absolute limits for vasopressor doses in shock states and no evidence that using “modest” doses of two or three vasopressors is superior to “high” doses of a single agent. When very high doses of vasoactive agents are required, consideration should be given to several specific and unaddressed causes of refractory hypotension, including intravascular volume depletion, adrenal insufficiency, profound acidosis, pericardial constriction or tamponade, and tension pneumothorax.

Brief high-dose corticosteroid therapy has consistently failed to improve outcomes in septic shock. Based upon the results of one actively debated study, the use of longer courses of lower-dose steroid therapy became commonplace. This study popularized the concept of “relative adrenal insufficiency,” defined by failure to increase serum cortisol levels by at least 9 μg/dL after a 250-μg dose of intravenous adrenocorticotropic hormone (ACTH). Mortality rates were reportedly reduced when ACTH “nonresponders” are treated for 7 days with a combination of hydrocortisone 50 mg q6h and fludrocortisone 50 mg/day. The results of this trial suggested that caution is indicated; “responders” given this steroid combination had nominally higher mortality rates than those not treated. The controversy over corticosteroid use has been fueled by a larger, randomized, blinded international multicenter trial that failed to confirm the benefits of corticosteroid in any group studied. Although each clinician will have a different interpretation of these results, the following strategy seems defensible. For patients with septic shock who respond to administration of fluid and low or modest doses of vasopressors, neither provocative adrenal testing
nor corticosteroid administration is indicated. For patients refractory to aggressive fluid replacement and moderate- or high-dose vasopressors, measurement of random plasma cortisol may be informative; if low, that is, true adrenal insufficiency, administration of glucocorticosteroid is indicated. If the baseline cortisol is in or above the expected normal range for severe stress, ACTH stimulation testing to identify a “nonresponder” is probably unnecessary. Nonetheless, because detectable response to steroid replacement occurs within hours in deficient patients and because 24 to 48 hours of stress dose steroid treatment is well tolerated, a brief therapeutic trial is warranted in desperately ill patients unresponsive to standard measures.

After initial resuscitation, a functioning brain, adequate (>0.5 mL/kg/h) urine output, evidence of adequate peripheral skin and digit perfusion, and a reasonable level of oxygenation and blood pressure are appropriate goals. These clinical perfusion goals usually are being met when cardiac output is in the 6- to 10-L/min range, arterial lactate concentrations are steadily declining, and oxygen delivery measurements are slightly above those for a resting healthy patient.

Glucose Control

For critically ill patients with stroke, myocardial infarction, and cardiac arrest, the development of hyperglycemia is associated with worse outcomes. High serum glucose concentrations impair neutrophil function and exert a procoagulant effect in patients with severe sepsis. Among postoperative patients, stringent control of glucose (80 to 110 mg/dL) appeared in several well-conducted studies to reduce the risk of developing severe sepsis and of dying compared patients managed in a more traditional glycemic range. This observation prompted numerous studies of strict glucose control that have failed to confirm the survival benefit initially observed among ICU patient categories distinct from the originally studied population. Several of these investigations have encountered a substantial incidence of hypoglycemia and attendant mortality risk. For most patients with sepsis, hypoglycemia is at least as hazardous as modest hyperglycemia. Furthermore, careful glycemic control is not a trivial undertaking; it usually requires a continuous insulin infusion with hourly monitoring of systemic blood glucose levels, entailing substantial labor expenditure.

Despite the conflicting data regarding benefits and risks, clinicians must make a practical decision regarding the boundaries of glucose regulation. At present, a prudent course of action is to maintain glucose levels near normal, probably in the 110 to 180 mg/dL range, monitoring their levels every 1 to 2 hours until stable and every 4 hours thereafter. Insulin dosing is prudent when two consecutive blood samples return glucose measurements greater than 180 mg/dL. To prevent hypoglycemia, frequent monitoring and measurements after changes in insulin doses are indicated. Careful attention should be given to patients who develop renal failure and those who have nutrition support discontinued because both populations are at particular risk for hypoglycemia.

Addressing Metabolic Acidosis

Lactic acidosis occurs commonly among sepsis patients. Fortunately, it is usually a mild and self-limited problem that resolves when intravascular volume deficits are corrected. When lactic acidosis results directly from low cardiac output, hypotension, and impaired perfusion, it is likely to be improved by increasing arterial pressure and measures taken to enhance circulatory flow. The benefits of fluids, vasoactive drugs, or red blood cells appear to be confined to resuscitation shortly after the onset of shock. Conversely, when cardiac output and arterial pressure are normal or high, no data convincingly demonstrate a benefit of further increasing output or oxygen delivery, especially in patients with established organ failures. In these, the ongoing problem may lie as much in mitochondrial (organelle) dysfunction as in impaired tissue perfusion. Survival correlates best with lactate levels and not serum pH; therefore, buffering an abnormal pH with sodium bicarbonate or dichloroacetate does not improve outcome, unless the underlying reason for lactate generation is corrected simultaneously. Even though experimental data
do not support the practice, as a practical matter, many physicians feel compelled to intervene when pH declines below 7.10, with the intention of enhancing myocardial performance and reducing elevated right ventricular afterload.

Support of the Kidney

It should not be overlooked that the kidney itself may be the source of sepsis, making it important to exclude urinary tract infection—especially that associated with obstruction. Even when not the instigator, the kidney commonly experiences short-lived dysfunction early in the septic process; more than 40% of patients develop transient oliguria, a condition usually reversed by simple fluid administration to correct underlying volume depletion. For patients with shock, a combination of volume repletion and vasoactive drug administration may be required to raise cardiac output and/or mean arterial pressure sufficiently to perfuse the kidney. There is no credible clinical evidence indicating that the use of dopamine (in any dose range) serves to protect the kidney from injury or improve outcome. Likewise, diuretic therapy has not been shown to improve outcome in oliguric patients. Perhaps the most important interventions to protect the kidneys of patients with sepsis are early circulatory resuscitation and avoidance of potentially nephrotoxic medications whenever possible. As renal function declines early in the septic process, any number of toxic drugs may accumulate to the point that they cause systemic toxicity or accentuate injury to the kidney. Probably, the most important class of compounds in this regard are antibiotics. Intermittent high-flow hemodialysis has been the traditional method for renal replacement therapy; however, continuous hemofiltration/hemodiafiltration (continuous renal replacement therapy [CRRT]) has become a popular alternative. Because continuous filtration avoids rapid fluid shifts, is less hemodynamically stressful than intermittent dialysis, and can remove large volumes of excess fluid after completion of the resuscitation phase, and can be performed in the ICU by bedside nurses, it has become the method preferred by many nephrologists and intensivists in such patients, especially for those with septic shock. Maintenance of effective CRRT may be troublesome, resource consuming, and relatively costly, however. Moreover, despite intuitive appeal, enthusiastic reports from some investigators and initially high expectations, no form of CRRT currently available has been confirmed to effectively clear the circulation of the noxious mediators that drive the seriously adverse outcomes of the septic response.

Nutritional Support

A thorough discussion of nutritional assessment and support is provided in Chapter 16. As with all other critically ill patients, there are two basic “truths” about nutrition. First, prolonged starvation (weeks to months) eventually proves fatal, and second, any patient can tolerate days without full feeding at goal intensity. Almost every other aspect of nutritional support is argued. Even with the disagreements about nutrition, there are some common practices. For better or worse, nutritional support usually is withheld until hemodynamic stability is achieved (1 to 2 days). Most practitioners now favor the enteral route of support because it provides more complete nutrition, helps preserves gut mucosa, contributes to acid buffering, offers some protection against profound hypoglycemia, and favorably impacts immune function. In addition, enteral nutrition is substantially less expensive than intravenous supplementation and avoids the complications associated with central venous catheters and hypertonic glucose solutions required for effective parenteral nutrition. At this time, there is no compelling evidence to suggest that any particular enteral feeding formula or particular balance of components is superior to another for the patient with sepsis, although there is some evidence to suggest that diets rich in omega-3 fatty acids may be beneficial. The place of probiotics and other means of restoring the normal microbiome has not yet been established. Simply stated, the current level of knowledge supports giving a balanced mixture of carbohydrate, protein, and lipid (based on the patient’s estimated needs) via an enteral route after hemodynamic stability is achieved. For patients with prolonged (>5 days) and profound gut dysfunction, partial or total parenteral nutrition may be indicated.
Directions in Detection and Treatment for the Near Future

Scientific understanding of the dysregulated pathobiology of sepsis and its most severe form, septic shock, as well as the best approaches to manage these conditions continues to unfold. Although fundamental principles seem unlikely to change, clinicians continue to struggle in some areas related to early detection, precise identification, and optimal intervention. What is clear, however, is that expression of this syndrome is not uniform, but rather shaped by genetic determinants, comorbidities, responsiveness to inflammatory stimuli, and the internal environment of the host, as well as by the virulence of the pathogen itself. Moreover, in any given individual the syndrome evolves continually over time, resulting in diversity that confounds current attempts to take a perfectly stereotyped approach to management. Nonetheless, we are making steady progress; for example, rapid antigen detection and same day DNA methodologies such as PCR have already helped aid the diagnostic process for some infections. Computer-assisted integration of physiologic, laboratory, and other key clinical information will likely help define phenotypes that reliably identify the nature and severity of organ dysfunction as well as their likely cause. Together with multichannel molecular signatures (transcriptomics, metabolomics, and proteomics), such innovations help form a foundation of precision or personalized medicine. Although most of these tools are still in their advanced development or early deployment phases, they hold clear promise eventually to bring biomarker assessment and disease course monitoring to higher levels, enabling more exact and helpful medical interventions and avoiding or minimizing the potential for iatrogenic harm.

SUGGESTED READINGS


Chapter 28
Thermal Disorders

• Key Points

1. Body temperature reflects the balance between heat generated and heat lost. Usually, heat loss is a much more efficient process than heat generation when environmental stresses act to displace body temperature from its normal set point.

2. The method of temperature measurement is important in recognizing fever or hypothermia. A thermistor-tipped pulmonary artery catheter that directly samples core temperature, though accurate, now is infrequently used. Oral and axillary temperatures are much less accurate because of problems of tachypnea and poor thermometer-body contact, respectively. A temperature-sensing urinary catheter is currently the most practical and reliable temperature monitoring device.

3. Hypothermia typically develops when patients compromised by infection, hypothyroidism, consciousness-impairing drugs or alcohol are exposed to cool ambient temperatures. Although controversial, passive external rewarming is probably the best treatment for most patients with initial temperatures at or above 32°C. Passive rewarming can be supplemented by heated humidified ventilator gas and warmed IV fluids. Over this range, external heating circuits are not usually necessary to achieve physiologic stability.

4. Exertional and nonexertional heatstrokes, though due primarily to environmental stress, often are complicated by underlying cardiovascular diseases, medications, or illicit drug use. Lowering the ambient temperature and spraying the patient with a windblown mist of tepid water are the most efficient methods to achieve rapid cooling. Fluid replacement is an adjunctive but frequently important measure. Fluid deficits of exertional hyperthermia are predictably greater than those of classic heatstroke.

5. Malignant hyperthermia, a potentially lethal syndrome precipitated by the use of inhalational anesthesia and neuromuscular blockade, must be considered as a cause of fever in the perioperative period. When the characteristic muscle rigidity and high fever are recognized, precipitating drug exposure must be terminated and a combination of external cooling and dantrolene initiated.

6. Neuroleptic malignant syndrome, another chemical-induced hyperthermic disease, can be caused by neuroleptic drug use or withdrawal of dopaminergic agents. Onset may occur at any time during drug exposure but is more common with the initiation of therapy or with a dosing increase. Termination of the offending drug and dantrolene therapy are indicated.

NORMAL TEMPERATURE REGULATION

Body temperature is normally tightly regulated between 36.2°C and 37.0°C. The net temperature reflects a balance between heat generated and heat lost. Heat dissipation occurs primarily by radiation and evaporation at the skin surface, with a lesser contribution from exhaled gas. When heat production rises (e.g., exercise) or heat loss declines (e.g., environmental exposure), sweating, cutaneous vasodilation, and hyperventilation attempt to return temperature toward normal. Behavioral responses (shedding clothing, drinking cool liquids, cessation of exercise, etc.) also serve to lower the temperature. If compensatory mechanisms fail to keep pace with heat generation, body temperature rises. Significant reductions in body temperature are usually the result of exposure to low ambient temperatures. Vasoconstriction and behavioral responses (donning extra clothing, seeking a warm environment, etc.) attempt to counteract excessive heat loss, but exercise and shivering are the only effective methods to amplify heat production. At rest, the trunk viscera (primarily the heart and liver) account for over 50% of heat produced;
during exercise, muscle activity may account for 90% of heat generation. Heat production may increase two- to fourfold with shivering and more than sixfold with exercise.

The anterior hypothalamus is responsible for temperature perception and the initiation of physiologic responses. Information is received from temperature-sensitive receptors in the skin, viscera, and great vessels as well as receptors in the hypothalamus. When a temperature increase is identified, hypothalamic modulation results in increased sweating (cholinergic response), cutaneous vasodilatation, and decreased muscle tone. A temperature decrease results in inhibition of sweating, cutaneous vasoconstriction, increased muscle tone, and shivering. In general, the body is much better adapted to losing excess heat than it is to rapidly producing it.

Aging impairs the ability to sense temperature extremes and blunts thermoregulation; thus, the elderly are at the highest risk for most temperature disorders. When cold, older patients are less able to generate heat because of decreased body weight and fat stores, decreased exercise and shivering capacity, and a reduced ability to vasoconstrict peripheral vessels. When hot, the elderly have impaired vasodilation. Older patients are also more likely to develop diseases that can either induce temperature changes (e.g., sepsis, hypothyroidism, renal failure) or impair their ability to respond to thermal challenges (e.g., peripheral vascular disease, depression, heart failure, and stroke). These very same conditions are likely to be treated with medications that further impair temperature sensing, regulation, and compensation. Finally, the elderly are most prone to financial barriers preventing environmental heating or cooling.

**TEMPERATURE MEASUREMENT**

**Types of Measuring Devices**

Mercury thermometers are usually unable to detect temperatures less than 34.4°C (94°F) or greater than 40.6°C (105°F) and fail to record values below the initial “shaken” level. Mercury thermometers respond slowly to temperature changes, making use of an electronic device or thermocouple (e.g., on a pulmonary artery catheter or indwelling urinary catheter) preferable when recording temperature extremes and rapid fluctuations. Infrared-sensing ear canal probes capable of accurate estimation of core temperature within seconds are now quite accurate. Plastic strip thermometers have limited accuracy and recording range.

**Sites of Measurement**

Regardless of which site is chosen, it is important to be consistent in measuring location and use of temperature units. If throughout the day the temperature is sometimes measured orally, other times in the axilla, and occasionally using an indwelling thermistor-tipped urinary catheter and is sporadically recorded in Fahrenheit and other times Centigrade degrees, confusion about temperature trends is sure to ensue.

In the nonintubated patient, measured oral temperatures are routinely less than their true value when respiratory rates exceed 18 breaths/min. Rectal temperatures avoid the artifacts of oral recordings because of varying respiratory rates, poor thermometer-patient contact, and aberrations caused by smoking or drinking hot or cold liquids. Although usually accurate, rectal temperatures may be spuriously low in patients with colonic impaction and may be slow to respond when rewarming the hypothermic patient if the temperature probe is lodged in cold luminal contents. Axillary temperatures often underestimate core temperature because of poor thermometer-skin contact and wide gradients between skin and core temperature. Obviously, a significantly elevated axillary temperature indicates fever. Esophageal measurement is an accurate “noninvasive” way to measure core temperature not commonly used because it requires specialized equipment. Infrared sensing of external ear canal temperature closely parallels core temperature and is not subject to influence by eating, drinking, or smoking as is oral temperature. The temperature of pulmonary artery blood may be continuously monitored using a thermistor-tipped pulmonary artery catheter and that of urine can be measured in the bladder using a thermistor-equipped indwelling catheter.
Although we speak of cooling and warming patients based on core temperature, it is important to recognize that the core temperature obtained through a thermistor urinary catheter, for example, does not guarantee identical temperatures in all body compartments.

**HYPOTHERMIA**

**Definition and Problems in Detection**

Patients with uremia, hypothyroidism, malnutrition, and congestive heart failure often have mildly reduced (1°C to 2°C) temperatures on their chronic baselines. In these patients, a “normal” or slightly increased temperature may represent fever. Clinical hypothermia, a core temperature below 35°C, sometimes escapes detection because symptoms are nonspecific and thermometers may fail to record in the appropriate range.

**Etiology**

Hypothermia can occur at any time of the year and is usually multifactorial in origin. Outdoor adventurers and the destitute are at highest risk. Among the latter group, environmental exposure following intoxication or a neurologic event is a common sequence of events. It is important to know that extreme ambient cold is not required to cause hypothermia, and a substantial number of cases occur at mild temperatures. Hypothermia may also be caused by medications that (1) alter the perception of cold, (2) increase heat loss through vasodilation, or (3) inhibit heat generation. (Phenothiazines and barbiturates are traditional offenders.) Common contributing metabolic conditions include adrenal insufficiency, hypoglycemia, and myxedema. Because hypothyroidism decreases heat production, blunts the shivering response, and impairs temperature perception, it is an etiologic factor in many cases of hypothermia. Hypopituitarism, severe sepsis, diabetic ketoacidosis, malnutrition, and mass lesions of the central nervous system (CNS) may also induce hypothermia. (The topic of hypothermic sepsis is discussed in [Chapter 27](#).) An intact skin covering and the ability to vasoconstrict are essential to the regulation of core temperature. Hence, both burns and spinal cord injuries impair the ability to conserve heat. Hypothermia is commonly observed during and immediately after general anesthesia because of the exposure of the body to low ambient temperatures and the use of drugs that blunt the vasoconstrictor response (e.g., neuromuscular blockers). An important iatrogenic source of hypothermia is administration of room temperature fluids in large quantities during resuscitation to patients who have already been exposed for examination.
Clinical Manifestations
Because physiologic changes are not precisely linked to specific temperature landmarks, it is best to classify hypothermia in broad categories: mild (32°C to 35°C), moderate (28°C to 32°C), and severe (<28°C). Vasoconstriction to conserve heat and shivering to generate heat are important initial compensatory mechanisms to prevent hypothermia. Unfortunately, both responses are blunted by a variety of underlying diseases or drugs and by profound hypothermia. Advancing hypothermia eventually depresses metabolism of all organ systems. Common physiologic events occurring during hypothermia are illustrated in Figure 28-1.

Cardiovascular
Mild hypothermia initially increases heart rate, blood pressure, and cardiac output through sympathetic stimulation. As temperature falls, heart rate and cardiac output decline as vasoconstriction maintains blood pressure. Moderate hypothermia decreases cardiac conduction and slows repolarization, prolonging all measured electrocardiographic (ECG) intervals and eventually causing atrioventricular (AV) nodal blockade. Characteristic deformations of the J point (Osborn waves) may be seen on the ECG but are neither sensitive nor specific indicators of core temperature. In advanced hypothermia, disproportionate reductions of cardiac output and blood pressure often
result in metabolic acidosis. Myocardial irritability, manifests by arrhythmias, increases as temperatures fall. Atrial fibrillation occurs commonly and usually converts to sinus rhythm on its own with rewarming. At temperatures less than 29°C, ventricular fibrillation may occur spontaneously or can be induced by movement or invasive procedures such as central venous catheter placement or nasogastric tube insertion. Ventricular fibrillation and other arrhythmias are extremely refractory to defibrillation and drug treatment until core temperature increases to approximately 30°C. Asystole supervenes as temperatures fall below 20°C.

**Neurologic**
Cerebral oxygen consumption is roughly halved for each 10°C (18°F) decline in temperature, greatly increasing the CNS tolerance of reduced perfusion. Initial CNS responses to hypothermia include decreased respiratory drive, lethargy, confusion, and fatigue. As temperatures fall below 32°C, hallucinations and a reduced level of consciousness are seen. Coma usually develops when core temperatures fall below 28°C, and at slightly lower temperatures, the EEG may even become electrically silent. Concurrent with the loss of consciousness, deep tendon reflexes disappear and the pupils become fixed. New asymmetric neurologic deficits rarely result from hypothermia alone, unless an independent CNS event (trauma or stroke) is the precipitant. Complete neurologic recovery is possible following an hour or more of asystolic cardiac resuscitation of patients with hypothermia.

**Renal**
Early in hypothermia, the combination of increased cardiac output, vasoconstriction, and renal tubular unresponsiveness to antidiuretic hormone produces a “cold diuresis.” The resulting large volume output of dilute urine (often with an osmolarity <60 mOsm/L) leads to intravascular volume depletion. Later in the course of hypothermia, volume contraction, a low cardiac output, and arterial vasoconstriction profoundly decrease renal blood flow. At temperatures below 27°C, most patients become anuric.

**Respiratory**
Hypercarbic respiratory drive generally decreases in parallel with reductions in temperature and metabolic rate. Suppressed hypercarbic sensitivity often allows respiratory acidosis to develop, even though hypoxic drive is preserved. As temperature approaches 30°C, oxygen consumption and CO₂ production are roughly halved. Early in hypothermia, the oxyhemoglobin dissociation curve shifts leftward, decreasing tissue oxygen delivery. Conversely, oxygen offloading is helped somewhat by lactic acidosis that results from hypoxia and reduced cardiac output. Despite these derangements, net oxygen delivery is often adequate for need, given the profound reductions in O₂ consumption. Altered consciousness and an increased volume of respiratory secretions warrant a low threshold for intubation.

Unnecessary controversy exists with regard to interpreting arterial blood gas (ABG) values in hypothermia. Standard practice is to warm ABG samples to 37°C for analysis. When this is done, higher partial pressures of oxygen (PaO₂) and carbon dioxide (PaCO₂) and lower pH values are observed than those that exist in vivo. To the naive physician, the reported ABG values may prompt poor clinical decisions: (1) the use of sodium bicarbonate to treat an artifactual acidosis, (2) overventilation in response to artifactual hypercarbia, and (3) withholding of supplemental oxygen because reported PaO₂ values appear adequate.

**Hematologic**
Hypothermia-induced diuresis decreases plasma volume, causing hemoconcentration and increased serum viscosity. The resulting sluggish blood flow predisposes to deep venous thrombosis. Total leukocyte counts are usually normal or slightly increased, but isolated granulocytopenia may be seen. Thrombocytopenia, a common finding, is believed to result from platelet sequestration. Hypothermia impairs coagulation enzyme activities leading to impaired intrinsic and extrinsic clotting function.
Local Cold Injury

Local cold injury includes frostnip, chilblains, flash freeze injury, and cold contact injury as well as frostbite. Frostnip and chilblains do not blister or necrose tissue and do not require surgical intervention. Flash freeze injury and cold contact injury is rarely circumferential but initiates rapid cooling creating large intracellular ice crystals which rupture and immediately kill affected cells. Frostbite, the most common form of injury, occurs with slower rates of cooling and may mimic laboratory cryopreservation where small ice crystals form initially in the extravascular space. Unlike flash freeze and cold contact injuries, soft tissues can potentially survive after thawing if vascular infarction is prevented.

Many factors increase the risk of cold injury. Alcohol and sedation decrease the awareness of cold and impair judgment necessary to seek shelter. Alcohol also inhibits shivering and causes cutaneous vasodilatation. The majority of civilian frostbite injuries are associated with neurologic impairment due to alcohol consumption, mental illness, or drug use. Smoking has also been implicated as increasing the risk of frostbite.

Brief exposure to near freezing skin temperature causes frostnip with pink skin but little acute damage. Rapid tissue cooling to freezing temperatures (flash freeze or cold contact injury) forms large intracellular and extracellular ice crystals leading to cell rupture and irreversible skin damage.

Frostbite occurs when intense vasospasm limits perfusion and cold injury progresses distally to proximally. This slow cooling produces small extracellular ice crystals preferentially in the extravascular fluid where protein concentrations are low. Extracellular electrolytes are concentrated, osmotically drawing water from adjacent cells. These deflated cells are less easily injured by the expanding extracellular ice crystals. Cellular metabolism slows and skin can tolerate decreased or absent blood flow for some periods of time. Blood flow usually resumes after thawing but may be diminished by edema, vasospasm, or thrombosis. The most effective treatment for acute frostbite is rapid rewarming. Clinically, return of blood flow is indicated by pink skin and warm digits. Large blisters form beneath damaged epidermis only where fluid leaks from perfused capillaries. Minimal blisters form where blood flow is absent and distal digits become gray or cyanotic often with hemorrhagic blisters forming proximally.

Other Complications

Hyperglycemia occurs commonly, as cold impairs pancreatic insulin release and increases counterregulatory hormone levels, including those of cortisol, epinephrine, glucagon, and growth hormone. Because it is relatively frequent and easily diagnosed and treated, hypothyroidism should be sought. Rhabdomyolysis may be seen reflecting skeletal muscle injury. Because hypothermia increases gastric acid production, it is sound to prescribe an acid-suppressing medication. Pancreatitis, ileus, and venous thrombosis are common. Although venous thrombosis often complicates hypothermia, subcutaneous heparin is poorly absorbed. Initially, therefore, pneumatic compression devices may offer a valuable option or adjunct for prophylaxis. Coexisting or precipitating infections (particularly pneumonia and meningitis) complicate many hypothermia cases. Cold-induced stiffness of the abdominal wall or neck often confounds clinical interpretation by simulating acute abdomen or meningitis.

Treatment

General Principles

Intubation may be needed for airway protection and delivery of supplemental oxygen. The orotracheal route is preferred, because of the risk of traumatic bleeding with other routes. However, muscle rigidity may limit mouth opening, and neuromuscular blockers are not likely to be effective at temperatures less than 30°C. In such cases, inserting a smaller tube with nasotracheal technique should be considered. Unfortunately, pulse
oximetry is not reliable as a guide to therapy in the setting of hypothermia and hypoperfusion.

Cardiopulmonary resuscitation should be initiated if the patient is pulseless (evaluate for 30 to 45 seconds) or has a nonperfusing rhythm. Effective chest wall compression may be impeded by muscle rigidity. Bradycardia is best managed by rewarming. Ventricular fibrillation should be treated by countershock even when the temperature is less than 32°C. If defibrillation is unsuccessful, rapid rewarming is a priority. Defibrillation can be reattempted with every 1°C to 2°C increase in temperature. Avoid intravenous drugs until temperature increases to approximately 30°C. Amiodarone may be a reasonable antiarrhythmic drug choice. Magnesium sulfate has also been used successfully. For patients with asystole, follow ACLS support guidelines and administer pharmacologic agents when the temperature approaches 30°C.

Hypothermic patients require fluids to address hypovolemia. Warm saline containing glucose is a good choice, as many of these patients may also be hypoglycemic. Vasoactive drugs have minimal effect on constricted vessels and increase the risk of rhythm changes. Although placement may not be feasible or function effective, fluid is preferably given via peripheral intravenous catheters, as thoracic central lines risk precipitating rhythm changes and femoral vein cannula placement risks significant local bleeding. Gastric tubes may be inserted as needed to relieve gastric distention. Routine laboratory studies include CBC, prothrombin and partial thromboplastin time, electrolytes, CK, and arterial blood gases.

Many deaths from hypothermia are iatrogenic, often caused by overly aggressive treatment. Rewarming, close observation, gentle patient handling, and a search for underlying causes are key factors in successful therapy. Because patients with mid-to-moderate hypothermia already are intensely vasoconstricted, exogenous pressors often serve only to induce arrhythmias. Fluids should be replaced as necessary to maintain blood pressure and vital organ perfusion. Peripheral intravenous lines, though safer, are difficult to place (because of vasoconstriction) and allow only sluggish infusion. However, special care should be taken not to advance central lines into the right atrium or ventricle, where they may stimulate life-threatening arrhythmias.

Serum amylase should be measured to detect pancreatitis—a complication which may be seen in severe cases. Hypothyroidism, a common precipitant of hypothermia, should also be sought. Because many patients either have infection as a precipitating cause or develop an infection as a result of the hypothermia, it is prudent to obtain cultures of blood, urine, sputum, and spinal fluid if clinically indicated and then begin empiric antibiotics. Empiric coverage should probably include that for pneumonia and bacterial meningitis if suspected. (Fortunately, such regimens will treat essentially all skin and urinary tract infections.) A gently inserted nasogastric tube is useful in management to counter gut hypomotility and can be used for rewarming gastric lavage. Because many medications have prolonged actions in hypothermia, all drugs must be given cautiously, particularly those that are hepatically degraded. Finally, it should be emphasized that prolonged resuscitative efforts (hours) can prove successful in hypothermia. Therefore, patients with hypothermia should be rewarmed to temperatures exceeding 29°C (85°F) before death is declared.

Rewarming

The aggressiveness with which hypothermia is reversed depends not only on the depth of temperature depression but also on the physiologic manifestations. Urgent rewarming assumes special priority in the setting of severe trauma that requires immediate surgical intervention. Caution must be exercised in reversing well-tolerated hypothermia. Because wet clothing can increase evaporative heat loss, it should be removed. Passive external rewarming with ordinary blankets is usually adequate if the temperature is higher than 33°C and typically results in temperature increases of 0.5°C to 2°C/h. Covering the head and neck is especially important, as these sites account for substantial heat loss. Historically, active external rewarming was controversial because it was believed to divert warm blood from the vital organs to the body surface and
return very cold blood from the limbs to the central core. This phenomenon, known as “afterdrop,” is likely to be unimportant provided external heating is continued until the core temperature normalizes. Active external rewarming can raise core temperature by as much as 1.5°C to 2.5°C/h. Advantages of this noninvasive method include wide availability of forced heated air devices. Warm water immersion is used less frequently in current practice and makes access to the patient difficult in the event of an emergency.

Internal rewarming may be performed by several methods. The simplest, universally available techniques are the administration of heated IV fluids and, for the intubated patient, inhalation of warmed humidified air. It makes sense to use only warmed fluids; administration of room temperature or colder solutions will lower the temperature further. The specific heat of water (1 kcal/kg°C) is slightly higher than that of the human body (0.83 kcal/kg°C); thus, administration of heated IV saline is a relatively efficient warming method. Obviously, this technique is limited by the maximum volume and temperature of fluid that can be administered. Because fluids can only be safely heated to 40°C to 42°C, each liter infused raises the patient's temperatures less than 1°C. Because it contains less water, warmed, fully humidified oxygen delivers heat more slowly, raising core temperature well less than 1°C/h. Although it is safe to deliver gas at temperatures up to 45°C, most commercial heaters limit gas temperatures at 41°C to 42°C.

Lavages of the stomach, bladder, colon, and pleural spaces have all been reported as potential methods of internal rewarming, but their effectiveness and safety are less clear. Peritoneal lavage with warmed fluid is another option for rapid core rewarming. Internal rewarming using dialysis or hemofiltration machines is also safe, effective, widely available method that can be rapidly instituted. Typically, temperature increases of 2°C to 3°C/h can be achieved. Cardiopulmonary bypass and the use of ECMO circuits are probably among the most rapid rewarming methods, but for obvious logistical and safety reasons, they are not the techniques of choice for most patients. Modern catheter-based rewarming systems are somewhat less effective than cardiopulmonary bypass but are a safe, convenient, and very efficient option. In studies conducted on injured patients, rapid rewarming using arteriovenous catheter techniques resulted in a significant decrease in blood product requirements, diminished need for crystalloid administration, and overall reduction in mortality. Another benefit attributed to these rewarming systems is support of the circulation.

**Management of Local Cold Injury**

After rewarming, patients with local cold injuries are treated with a conservative regimen including bedrest, oral ibuprofen, and deflation of any bullae which appear. A subset of patients with poor prognostic findings including cool skin after rewarming, numbness, dusky or blue digits without bullae, or hemorrhagic proximal bullae are considered for angiography with instillation of thrombolytic agents in an attempt to restore distal perfusion. Relative contraindications to thrombolytic therapy include recent stroke or trauma, recent surgical procedures, bleeding tendency, >24 hours of warm or cold ischemia, and evidence of a freeze/thaw/refreeze pattern. Figure 28-2 demonstrates serial angiography from a patient presenting with frostbite to fingers. Note hemorrhagic blisters and the evolution in angiogram findings. Thrombolytic therapy represents aggressive treatment for frostbite injury and should be considered only in experienced centers.
FIGURE 28-2. Cold Injury with Frostbite. A: Angiogram on hospital day 1 with perfusion defect proximal to the right palmar arch and at the level of the left wrist. B: Final angiogram after thrombolytic therapy completed on hospital day 4 with distal blush present on the thumb and third through fifth digits bilaterally and flow to the distal interphalangeal joints. C: Hands after completion of thrombolytic therapy. D: Hands several weeks after completion of thrombolytic therapy. No amputations were required. (From J Burn Care Res. 2016;37:e323-e334.)

Patients with Cardiovascular Instability

The primary therapeutic goal in patients with lifethreatening arrhythmias should be rewarming the core quickly to temperatures greater than 29°C, a threshold below which defibrillation and antiarrhythmic therapy are often ineffective. There are no controlled trials demonstrating superiority or even effectiveness of one antiarrhythmic agent over others. Transvenous pacemakers increase myocardial irritability and the risk of ventricular fibrillation. Therefore, they should not be used in the absence of a clear indication. If pacing is considered unavoidable, transvenous pacers should be used only after transthoracic pacing has failed. For the profoundly cold patient suffering cardiac arrest, cardiopulmonary bypass represents an attractive option in
which perfusion and rewarming occur simultaneously.

**Diagnosis of Death**

Prolonged resuscitative efforts (even lasting hours) can prove successful in hypothermia, and survival after core temperatures as low as 14°C has been reported. Therefore, unless there are obvious other lethal injuries or the victim is frozen solid, patients with hypothermia should be rewarmed to temperatures greater than 32°C before death is declared. Severe hyperkalemia (>10 mEq/L) may represent a surrogate marker for death.

**HYPERTERMIA**

**Causes of Temperature Elevation**

In the intensive care unit (ICU), sudden temperature elevations usually signal infection, making it prudent to perform a directed physical examination and, if indicated, obtain appropriate cultures and institute empirical antibiotics. Although infection is the most common explanation, several life-threatening noninfectious causes of fever are frequently overlooked (Table 28-1). Interestingly, fever in ICU patients often responds unpredictably to acetaminophen; nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) are often more effective.

**SYNDROMES OF EXTREME HYPERTERMIA**

Regardless of etiology, high temperatures injure cells. In humans, as little as an hour at core temperatures greater than 40°C (105°F) may damage the CNS, producing behavioral changes, delirium, and confusion that progresses to cerebellar dysfunction, decerebrate rigidity, seizures, and coma. Temperatures higher than 50°C (120°F) can cause devastating injury quite rapidly. Other organ system changes include vasodilatation with reflex tachycardia and compensatory vasoconstriction in the splanchnic and renal vascular beds. A variety of electrocardiogram changes have been described, including conduction defects, prolonged QT intervals, and nonspecific ST and T wave changes. High fevers should be reduced to safer levels as quickly as possible. On the other hand, there are little, if any, data to suggest that reducing temperatures below 40°C is routinely necessary and attempts to do so quickly may prove detrimental.

<table>
<thead>
<tr>
<th>Table 28-1. Noninfectious Causes of Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heatstroke</td>
</tr>
<tr>
<td>Neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>Malignant hyperthermia</td>
</tr>
<tr>
<td>Drug allergy</td>
</tr>
<tr>
<td>Transfusion reaction</td>
</tr>
<tr>
<td>Autonomic insufficiency</td>
</tr>
<tr>
<td>Malignancy</td>
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<tr>
<td>Stroke or CNS hemorrhage</td>
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</tbody>
</table>
Four noninfectious conditions producing high fever in the ICU include (1) classic or nonexertional heatstroke, (2) exertional heatstroke, (3) malignant hyperthermia, and (4) neuroleptic malignant syndrome (NMS), and (5) Serotonin Syndrome (SS). All are associated with dramatic elevations in core temperature and demand rapid recognition and therapy. Clinical features, etiology, and treatment of these diseases are contrasted in Table 28-2. The related problems of anticholinergic and stimulant toxicity and serotonin syndrome are also discussed in Chapter 33 and that of thyroid storm in Chapter 32.

### Table 28-2. Features of Heatstroke, NMS, and Malignant Hyperthermia

<table>
<thead>
<tr>
<th>Feature</th>
<th>Malignant Hyperthermia</th>
<th>Neuroleptic Malignant Syndrome</th>
<th>Classic Heatstroke</th>
<th>Exertional Heatstroke</th>
<th>Serotonin Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usual age</strong></td>
<td>Children and young adults</td>
<td>Young adults</td>
<td>Elderly</td>
<td>Any age</td>
<td>Any age</td>
</tr>
<tr>
<td><strong>Common precipitants</strong></td>
<td>Succinylcholine, halogenated anesthetics</td>
<td>Neuroleptics</td>
<td>Diuretics, tricyclics, anticholinergics</td>
<td>Hot environment Confining garb</td>
<td>Drug enhancing central serotonin activity</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Abnormal muscle calcium metabolism</td>
<td>Reduced brain dopamine levels</td>
<td>Impaired heat loss</td>
<td>Impaired heat loss</td>
<td>Receptor overstimulation</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>Remove offending drug Dantrolene</td>
<td>Remove offending drug Dantrolene</td>
<td>External cooling</td>
<td>External cooling Fluid replacement</td>
<td>Remove offending agent, symptomatic treatment</td>
</tr>
</tbody>
</table>

### Nonexertional (Classic) Heatstroke

**Definition and Clinical Presentation**

Classic heatstroke is a potentially lethal disorder that should be suspected in patients exposed to high ambient temperatures who exhibit the triad of (1) fever higher than 40°C (105°F), (2) hot dry skin, and (3) CNS dysfunction. The cognitive abnormalities may include lethargy, delirium, seizures, cerebellar dysfunction, and coma. An
antecedent history of physical activity is usually absent. Tragic cases of children locked in automobiles for just minutes illustrate how rapidly heatstroke can occur when ambient temperatures reach 43°C to 54°C. Tachycardia and tachypnea are nearly universal, and hypotension afflicts about a quarter of victims. Other organ systems (renal, hematologic) are frequently affected, but their involvement is not necessary for diagnosis.

**Mechanisms**

When temperature rises, cardiac output usually increases, cutaneous vasodilation occurs, blood flow is redirected from the core to the surface, and sweating begins. Evaporation of sweat normally is responsible for more than 50% of heat dissipation, but high humidity and poor air circulation impair the efficiency of this process. The huge capacity for heat dissipation is evidenced by the facts that evaporation of less than 2 mL of sweat results in more than a kilocalorie of heat loss and humans are capable of up to 2 L of sweat production per hour. When compensatory mechanisms cannot shed sufficient heat, temperature rises.

In the past, heatstroke was believed to be a simple process of direct cellular damage from high temperatures, but in recent years, it has become clear that the disease is mechanistically complex. In fact, heatstroke shares cardinal pathophysiologic features of severe sepsis such as activation of clotting progressing to DIC and generation of proinflammatory cytokines such as tumor necrosis factor and interleukin-1. Collectively, these processes lead to endothelial cell damage and microvascular thrombosis that result in organ failures.

**Causes**

Nonexertional heatstroke can occur in anyone but is most common among the elderly because of five predispositions to impaired heat dissipation. These include (1) decreased sweat production, (2) decreased skin blood flow, (3) limited cardiac compensation, (4) impaired hypothalamic regulation, and (5) use of drugs that impair heat loss. Old, poor, and urban residents are at the highest risk by virtue of the fact that they may not be able to afford to cool their homes and do not feel safe enough to leave doors and windows ajar.

Among younger people, prescription or illicit drug use is a common contributing factor. CNS tumors, stroke, and certain drugs (e.g., cocaine, ecstasy [MDMA], lysergic acid diethylamide [LSD], amphetamines) may disrupt hypothalamic heat regulation. Other drugs may produce heatstroke through increased heat generation (e.g., cocaine, tricyclics, lithium, or alcohol withdrawal), by impairing heat loss (e.g., anticholinergics, phenothiazines, diphenhydramine, diuretics, and tricyclic antidepressants) or by a combination of these two mechanisms. Impaired heat loss may also be seen with extensive burns or skin diseases (e.g., scleroderma) and with the use of occlusive dressings or ointments that cover large skin areas.

**Laboratory Studies**

ABGs typically reveal a pure respiratory alkalosis. Occasionally, lactic acidosis is superimposed, but it is rather uncommon (unlike exertional heatstroke). Hypophosphatemia and hypokalemia occur frequently. Although rhabdomyolysis may result in hyperphosphatemia, hypocalcemia, hyperkalemia, elevations in creatine phosphokinase (CPK) and serum aspartate aminotransferase (AST), and rhabdomyolysis, such consequences are not routine. (Again, they are much more prevalent in exertional heatstroke.) Although most patients have subclinical coagulation changes (e.g., elevated D-dimers, reduced protein C levels), overt disseminated intravascular coagulation is uncommon.

**Complications and Prognosis**

Heatstroke can result in the failure of any organ system, and unfortunately, many heatstroke victims sustain permanent brain injury. Acute respiratory distress syndrome, pancreatitis, hepatic failure, and bowel ischemia have been described. Of all vital organs, the kidney is at highest risk of injury from ensuing dehydration, hyperuricemia, and rhabdomyolysis, all of which occur more commonly with exertion-related hyperthermia.
**Treatment**

With the exception of therapy to rapidly lower temperature, the treatment of heatstroke is supportive. Core temperature should be lowered to below 41°C as quickly as possible. The most effective method of cooling is combining convection and evaporation, not conduction. Spraying unclothed victims with tepid water (15°C to 20°C) and using a fan to promote evaporation cool most patients to less than 40°C within 60 minutes. Ice packing or cold water immersion produces conductive heat loss rapidly but has major limitations apart from the difficulty of implementation. Attempts at conductive cooling result in intense peripheral vasoconstriction and shivering, which serve to sustain core temperature. Now, a variety of commercially available intravascular and surface cooling devices are used that reliably lower the body temperature but often at substantial cost. In addition, there is little evidence that such devices are safer or yield superior clinical outcomes to lower technology approaches. Regardless of the cooling method, patients should be monitored closely for temperature rebound after initial control.

Fluid deficits in adults with classic heatstroke average just 2 L, but the extent of volume depletion is highly variable. If hypotension is present, more aggressive fluid replacement, perhaps guided by central venous pressure monitoring, should be undertaken. Cooling the infused fluids below room temperature, perhaps as low as 4°C, is a simple adjunctive method of temperature reduction. α-Agonists and atropine should be avoided if possible because drug-induced peripheral vasoconstriction further impairs heat loss. Dantrolene has been shown to be ineffective.

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**Exertional Heatstroke**

**Definition and Clinical Presentation**

In distinction to its nonexertional counterpart, exertional heatstroke is diagnosed when the triad of (1) fever higher than 40°C (105°F), (2) hot dry skin, and (3) CNS dysfunction occur in the setting of strenuous physical exertion.

**Causes**

Exertional heatstroke is usually the result of vigorous physical exercise by an otherwise healthy person in a hot humid environment; however, exercise alone can initiate the syndrome. Victims of exertional heatstroke are commonly involved in activities they continue long after perceiving the sensation of extreme heat (e.g., military training, firefighting, law enforcement, athletic activity). Furthermore, these patients often are wearing heavy or restrictive equipment that impairs heat loss. In addition to environmental stress, predisposing factors include dehydration and lack of training and acclimatization. In recent years, several deaths have been linked to the concurrent use of stimulants (e.g., cocaine, amphetamines) or over-the-counter weightloss drugs (e.g., ephedra) during athletic training.

**Clinical Features**

Clinical features include fever, altered mental status, hypotension, tachycardia, and tachypnea. Laboratory data frequently suggest a diagnosis of rhabdomyolysis with elevated AST, CPK, and myoglobinuria. Renal function tests are often abnormal as a result of dehydration and rhabdomyolysis. Hemoconcentration can be profound and tends to be more frequent and severe in exertional than classic heatstroke because of the greater fluid losses. Thus, fluid replacement using cooled isotonic crystalloid is indicated. When intravascular volume status is uncertain, monitoring the central venous pressure may be helpful.

**Treatment**

Exertional heatstroke can be prevented through acclimatization, appropriate dress, modification of work or...
exercise schedules, and adequate hydration. Therapy includes discontinuing activity, moving the patients to a cooler location, rehydration, and external cooling. As with nonexertional heatstroke, removal of clothing and spraying the patient with tepid water appear to be the most effective methods to rapidly lower the temperature. Blowing a fan across the disrobed victim accelerates evaporative heat loss. Dantrolene is not effective.

**Outcome**

With contemporary management, survival from heatstroke approaches 90%. Morbidity relates to duration of hyperthermia and to underlying conditions. Advanced age, hypotension, coagulopathy, hyperkalemia, acute renal failure, and prolonged coma are associated with poor prognosis. Elevated lactate levels portend a poor prognosis in classic heatstroke but not in exertional heatstroke. Rapid cooling (<1 hour) reduces mortality risk.

**Malignant Hyperthermia**

**Causes**

Malignant hyperthermia is a rare but dramatic heritable disorder caused by excessive heat generation resulting from dysfunctional calcium channels in skeletal muscle and impaired calcium-mediated contraction coupling. Proclivity to malignant hyperthermia is genetically transmitted as an autosomal dominant trait and occurs in 1 in 50 to 1 in 150,000 adults who receive anesthesia. Inhaled anesthetics and succinylcholine cause the vast majority of cases, although neuromuscular blockers, ethanol, caffeine, sympathomimetics, parasympathomimetics, cardiac glycosides, and quinidine analogs have been implicated as contributors. Infection, physical or emotional stress, anoxia, and high ambient temperature may also precipitate malignant hyperthermia. Nondepolarizing neuromuscular blockers, etomidate, nitrous oxide, ketamine, opiates, benzodiazepines, propofol, and local anesthetics are considered safe to use in patients with malignant hyperthermia. Malignant hyperthermia is distinctly more common among young people, especially those with a history of congenital myotonia or a muscular dystrophy.

**Clinical Diagnosis**

The diagnosis is a clinical one recognized by the presence of (1) muscular rigidity, (2) high (commonly 41°C to 45°C) and rapidly rising fever (often 2°C/min), and (3) acidosis that occurs in an appropriate clinical setting. Although temperature may begin rising within minutes of drug exposure, hyperthermia can be delayed up to 12 hours. Therefore, the condition should be considered in the differential diagnosis of early, severe postoperative fever. Extreme muscle activity massively increases oxygen consumption and CO\(_2\) production; the resulting tissue hypoxia eventually leads to lactate formation. Hence, a combined metabolic and respiratory acidosis is frequently seen. Tachycardia, tachypnea, ventricular arrhythmias, and skin mottling are common clinical signs. Phosphate, sodium, potassium, uric acid, and muscle enzymes (CPK, lactic dehydrogenase [LDH], and aldolase) are routinely elevated as a result of rhabdomyolysis.

**Complications**

Massive increases in metabolic rate cause hypercapnia, hypoxemia, and hypoglycemia in a large percentage of cases. When not promptly treated, malignant hyperthermia can produce severe muscle damage with necrosis and soft tissue calcification. Renal injury resulting from circulating myoglobin may be attenuated or even averted by alkalinizing the urine and by maintaining blood pressure and renal tubular flow. High cardiac output with low systemic vascular resistance may result in hypotension, but \(\alpha\)-agonists should be used cautiously because vasoconstriction may retard heat loss.
Direct thermal toxicity may cause neuronal death. The hippocampus and the Purkinje cell layer of the cerebellum are particularly vulnerable, accounting for movement disorders after recovery. Prophylactic anticonvulsants may prevent the seizures that occur in many cases. Likewise, histamine blockers or proton pump inhibitors are indicated to counteract the tendency for GI hemorrhage. Although transaminase elevations are common, hepatic necrosis is infrequent. Late hematologic effects include increased leukocyte and platelet counts, coagulopathy resulting from impaired liver function, and direct thermal activation of platelets and clotting factors.

**Treatment**

Malignant hyperthermia is a true emergency with mortality proportional to the magnitude and duration of peak temperature. Even brief delays in therapy may prove fatal. Temperature should be continuously monitored until it stabilizes below 39°C. Exposure to potentially offending volatile anesthetics and neuromuscular blocking agents must be stopped as soon as feasible, and it is wise to terminate any operative procedure if possible. In the exceptional case where a surgical procedure cannot be aborted, drugs believed to be safe include nitrous oxide, barbiturates, benzodiazepines, pancuronium, and opiates. Ventilation with 100% oxygen should be started immediately. Direct external cooling with a fanned water mist dissipates heat while awaiting definitive therapy with dantrolene. Shivering caused by external cooling can be controlled with benzodiazepines and nondepolarizing neuromuscular blockers.

Dantrolene stops the runaway heat generation by inhibiting calcium release from sarcoplasmic reticulum. Doses of 2.5 mg/kg should be initiated swiftly and can be repeated at 5-min intervals until symptoms subside or a maximum safe dose of 10 mg/kg is reached. As a rule, improvement occurs quickly if recognition and treatment are prompt. (Failure to improve with doses of 10 mg/kg should raise questions about the diagnosis.) Subsequent doses of 1 mg/kg every 4 to 6 hours should be continued for 36 to 48 hours. If dantrolene is ineffective or takes effect slowly, surface cooling methods may be used. By inhibiting calcium release, dantrolene can cause muscle weakness, perhaps even sufficient to impair spontaneous ventilation. Thus, an extra measure of caution should be exercised in extubating patients treated with dantrolene.

Because patients with malignant hyperthermia usually have normal intravascular volume, fluid requirements are minimal. Although debated, fluid loading to promote urine flow and serum alkalinization with sodium bicarbonate may be useful to prevent myoglobinuric renal tubular injury. Hyperkalemia can be treated initially in a conventional manner using sodium bicarbonate for pH correction, insulin and glucose to transfer potassium into cells, and calcium to stabilize membranes (see Chapter 13). Non-hyperkalemia-related arrhythmias are best treated by controlling the underlying disorder, although lidocaine and β-blockers may be useful. Because this disorder involves calcium metabolism abnormalities, avoid calcium channel blockers.

**Neuroleptic Malignant Syndrome (Drug-Induced Central Hyperthermia)**

**Definition**

Like malignant hyperthermia, the more frequently encountered NMS is a drug-associated hyperthermic syndrome characterized by fever, muscle rigidity, and altered mentation and frequently accompanied by pulmonary dysfunction and autonomic instability. It differs, however, regarding predisposition, precipitating factors, underlying mechanism, time course, prognosis, and patient substrate. The differential diagnosis of neuroleptic NMS includes heatstroke, thyroid storm, tetanus, pheochromocytoma, anticholinergic or lithium toxicity, delirium tremens, monoamine oxidase (MAO) inhibitor crisis, and the serotonin syndrome.
Causes
The precise mechanism of NMS is unknown, but its genesis involves some combination of drug-induced changes in dopamine levels in the brain and skeletal muscle of susceptible individuals. Two lines of clinically relevant evidence support this conclusion. The first is that antipsychotic drugs that decrease dopamine’s inhibitory effects on serotonin-mediated heat generation or that directly alter brain serotonin levels have been associated with the condition. The second line of evidence is that abrupt withdrawal of anti-Parkinsonian agents (dopaminergic agents), such as levodopa-carbidopa and amantadine, may precipitate the disease. The association of NMS with discontinuation of dopaminergic drugs is mechanistically interesting because dopaminergic drugs not only act in the brain but also have direct muscular-relaxing properties. Oddly, there are no reports of NMS following abrupt cessation of prolonged dopamine infusions. For unclear reasons, dehydration and extreme muscular activity predispose to NMS.

The association of NMS with neuroleptics is unarguable, and the typical antipsychotics (e.g., haloperidol, chlorpromazine, fluphenazine) are thought to be more likely to cause the syndrome than are the atypical antipsychotics (e.g., clozapine, olanzapine, risperidone). NMS occurs in only a tiny minority of those exposed to neuroleptics. Patients developing the disease when treated with one antipsychotic are unlikely to manifest the syndrome when treated with another, despite an ostensibly identical mechanism of action, and there does not appear to be a clear dose-risk relationship. Furthermore, NMS can occur at any time a patient is receiving a neuroleptic and has even been reported up to 3 weeks after discontinuing therapy. Moreover, although many cases have been identified following an increased neuroleptic dosing, there are numerous reports linking NMS to antipsychotic withdrawal. Interestingly, even though abrupt changes in neuroleptic doses are routine in the ICU, NMS has rarely been reported. NMS shares some features with malignant hyperthermia. Many NMS victims have been found to have abnormalities in skeletal muscle calcium release, and most respond to the calcium modulator dantrolene. Although the degree of crossover between malignant hyperthermia and NMS is unknown, some patients who have had malignant hyperthermia undergo uneventful therapy with neuroleptic drugs.

Clinical Features
Rapid onset of fever higher than 38°C, altered mentation, muscle rigidity, delirium, tachycardia, unstable blood pressure, diaphoresis, and extrapyramidal movements characterize the syndrome. In most cases, extrapyramidal symptoms antedate the fever and autonomic abnormalities. As is evident, clinical features alone may not distinguish this syndrome from malignant hyperthermia (especially in a postoperative patient treated with haloperidol). Symptoms develop over 24 to 72 hours and may last for 1 to 3 weeks. Even with optimal treatment, NMS is fatal in a significant minority of cases and is frequently complicated by rhabdomyolysis, acute myocardial infarction, and persistent movement disorders.

Laboratory
Laboratory abnormalities are all nonspecific and include leukocytosis and elevated values for CPK, BUN, creatinine, and liver transaminases. Lumbar puncture and head computed tomography are not diagnostic but may be necessary to exclude mass lesions and infections from the differential diagnosis.

Treatment
The initial treatment of NMS requires stopping the suspected offending drug and beginning external cooling. All neuroleptics and dopamine antagonists, such as metoclopramide, should be withheld at least until the disease abates. Intravascular fluids should be administered based on estimated deficits, blood pressure, pulse and urine output values, or central venous pressure measurements. The effectiveness of pharmacologic therapy for NMS is far less certain than for malignant hyperthermia, and there are no comparative trials of the
advocated treatments. Dantrolene (2.5 mg/kg IV every 5 minutes up to approx. 10 mg/kg) has been recommended until hyperthermia and excessive muscular activity are corrected. Unfortunately, there are little, if any, data about the optimal duration of therapy. Dantrolene given by peripheral IV may cause chemical phlebitis because of its profound alkaline pH. Bromocriptine, a dopamine agonist, in doses of 2.5 to 10 mg given three times daily, has been reported as an effective alternative to dantrolene. Bromocriptine controls rigidity and fever within hours, but dosing may be limited by its most common side effects, hypotension, and delirium. Success has also been reported using combinations of the anti-Parkinson drugs levodopa-carbidopa and amantadine.

Serotonin Syndrome (SS)

Etiology
In a manner similar to NMS, use of serotonergic drugs including selective serotonin uptake inhibitors is known to cause the SS. Serotonin is a neurotransmitter involved in circuits controlling the sleep wakefulness cycle, mood, and thermoregulation. SS which presents a combination of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities is caused by overstimulation of serotonin receptors.

A number of drugs may produce SS. For example, L-tryptophan causes increased serotonin synthesis while agents such as linezolid and ritonavir decrease serotonin breakdown. Serotonin release is increased by agents such as amphetamines and cocaine. Serotonin reuptake is decreased by commonly used agents such as meperidine, fentanyl, and tramadol. Other agents which may decrease serotonin reuptake are the broader category of serotonin reuptake inhibitors. Finally, serotonin receptor agonists may cause serotonin syndrome. LSD, lithium, and buspirone may cause serotonin syndrome by this mechanism.

Treatment
Presentation of SS may be impressive with symptoms including mental status changes, autonomic hyperactivity, mydriasis, tachycardia, hypertension, hyperthermia, and diaphoresis, and neuromuscular changes including hyperactive tendon reflexes, rigidity, and clonus. The most important intervention is removal of the responsible agent. Symptoms should abate within 24 hours of intervention. Benzodiazepines and serotonin agonist cyproheptadine are also thought effective specific therapies. Other treatment is symptomatic (Table 28-2).

SUGGESTED READINGS


Sawamoto K, Bird SB, Katayama Y, et al. Outcome from severe accidental hypothermia with cardiac arrest

**Key Points**

1. The development of acute kidney injury is associated with a significant increase in mortality in the critically ill patient despite existence of dialytic support capable of replacing a significant portion of the filtering function of the kidney. Because no specific therapy exists for treating acute kidney injury, prevention is critical.

2. Prerenal azotemia and obstructive uropathy are rapidly reversible causes of acute kidney injury that should be sought in every case and aggressively treated.

3. Acute kidney injury not caused by prerenal or postrenal causes is commonly the result of combined hypoperfusion and drug-induced injury.

4. Medications need to be carefully selected and adjusted for the degree of renal insufficiency.

5. For many patients, intermittent conventional hemodialysis represents the best option for managing fluid status, uremia, and electrolyte and acid-base disorders. If fluid overload is the predominant problem, or the patient is hemodynamically unstable, continuous renal replacement therapy represents a reasonable alternative.

6. When acute renal failure occurs in a patient with previously normal kidneys, renal function can usually be expected to return to near baseline levels, after the critical phase of illness.

The kidney's excretory function can be replaced mechanically, and its metabolic functions can be compensated by the actions of the lung, liver, and drugs. Therefore, the kidney is the only major organ whose total failure is not necessarily fatal. Yet, the development of acute kidney injury (AKI) in a critically ill patient is associated with significant morbidity and mortality. A greater appreciation of the importance of maintaining adequate perfusion and avoiding nephrotoxic compounds might have reduced the incidence and severity of AKI but for the expansion of an aging population with diabetes and hypertension. Fortunately, the safety and efficiency of renal replacement therapy (RRT) have improved, permitting treatment of patients who previously would have not been candidates.

**EPIDEMIOLOGY**

AKI occurs in approximately 7% of all hospitalized patients and afflicts between one third and two thirds of critically ill patients, depending on AKI definition and the type of practice. Reported mortality increases proportionately with increasing severity of renal insufficiency. In ICU patients requiring RRT, mortality has been reported as high as 50% to 70%. Although the need for RRT is a recognized risk factor for in-hospital mortality, even small changes in serum creatinine are associated with increased risk of death. Morbidity, a less appreciated consequence of AKI in the ICU, is associated with increased cost, length of stay, and risk of initiating chronic kidney disease.

**INDICES OF RENAL FUNCTION AND INJURY**

**Urine Volume**

Urine volume usually tracks kidney perfusion, whereas urine specific gravity and osmolality parallel concentrating
ability (tubular function). Therefore, renal blood flow is probably adequate in nonoliguric patients, and patients producing concentrated urine are unlikely to have significant tubular damage. However, it is important to note that concentrated urine does not imply normal perfusion; the standard response of the kidney to inadequate perfusion is to concentrate the urine. Certain calculated indices have long been used to distinguish problems of perfusion from those of tubular dysfunction, but all of these measures have a much lower specificity than commonly believed (Table 29-1).

<table>
<thead>
<tr>
<th>Table 29-1. Laboratory Indices in Acute Renal Failure</th>
<th>Prerenal</th>
<th>Intrarenal</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN/creatinine</td>
<td>&gt;10:1</td>
<td>Approx. 10:1</td>
</tr>
<tr>
<td>Urinary Na⁺ concentration</td>
<td>&lt;20 mEq/L</td>
<td>&gt;40 mEq/L</td>
</tr>
<tr>
<td>Urine specific gravity</td>
<td>&gt;1.020</td>
<td>1.010-1.020</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>&gt;500 mOsm/L</td>
<td>&lt;300-400 mOsm/L</td>
</tr>
<tr>
<td>Urine creatinine/plasma creatinine</td>
<td>&gt;40</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Urine Na⁺/creatinine clearance</td>
<td>&lt;1</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Na⁺ clearance/creatinine clearance (FENa)</td>
<td>&lt;1</td>
<td>&gt;3 (1-3 indeterminant)</td>
</tr>
<tr>
<td>Urine sediment</td>
<td>Normal or hyaline casts</td>
<td>Granular casts</td>
</tr>
</tbody>
</table>

**Blood Urea Nitrogen**

Because the kidney is the primary filter of nitrogenous waste, blood urea nitrogen (BUN) and creatinine track renal function but do so imperfectly. The extreme variation of urea load and the ability of the proximal tubule to absorb filtered urea render BUN less reliable than creatinine for this purpose. For example, rhabdomyolysis, increased protein ingestion, gastrointestinal (GI) bleeding, and corticosteroid use may all increase the BUN, whereas liver disease, low-protein diets, or low muscle mass decrease BUN. In addition, when urine flow declines because of volume depletion, the BUN rises disproportionately, as it is reabsorbed along with sodium and water. Conversely, when glomerular filtration rate (GFR) is increased such as in pregnancy and during aggressive volume resuscitation, the BUN declines. As general guidelines, the BUN increases by 10 to 15 mg/dL/d and creatinine by 1 to 2.5 mg/dL/d after abrupt renal shutdown. The serum potassium (K⁺) usually rises less than 0.5 mEq mg/dL/d, and bicarbonate (\(\text{HCO}_3^-\)) falls by about 1 mEq/L/d under the same conditions. Under the catabolic stress of burns, trauma, rhabdomyolysis, steroids, severe sepsis, or starvation, the rates of change of these parameters may be doubled.

**Creatinine**
In contrast to BUN, daily creatinine production is more consistent. Patients with low muscle mass from starvation, limb amputation, or neuromuscular disease and those with a protein-restricted diet have on average lower creatinine values than patients with conventional diets and body composition. A rising creatinine indicates that the rate of production exceeds its combined clearance by filtration and proximal tubular secretion because the kidney does not reabsorb or metabolize creatinine. For these reasons, a stable elevation of creatinine implies that a new steady state has been achieved at a decreased GFR. The best method to determine GFR is a 24-hour urine collection, but logistical problems, the inherent delay imposed, and the high incidence of severe oliguria usually make this impractical. Consequently, GFR is typically estimated using the modification of diet in renal disease (MDRD) equation: GFR (mL/min/1.73 m²) = 170 × (Serum creatinine)⁰.⁹⁹⁹ × age (years)⁰.₁₇₆ × 0.762 (if female) × 1.8 (if African American) × BUN (mg/dL)⁰.₁₇₀ × albumin (g/dL)⁰.₃₁₈. It is important to understand that because serum creatinine increases lag behind the deterioration in actual GFR, kidney function cannot be reliably assessed until creatinine stabilizes. For this reason, drug doses are usually overestimated by the calculated GFR during the evolution of AKI. Thus, if a patient becomes anuric or severely oliguric, it is probably best to estimate drug dosing based on a GFR of zero. Without intervention, creatinine usually plateaus at 12 to 15 mg/dL, depending on catabolic state and muscle mass. (Rhabdomyolysis may cause creatinine to exceed this value.)

Normally, about 15% of urinary creatinine is secreted by the proximal tubule (a higher fraction in renal failure). As a result, drugs that compete with creatinine for tubular secretion may result in a true increase of serum creatinine despite a preserved GFR. Serum and urinary creatinine values are functions of lean body mass in normal persons and show little or no response to changes in diet. Because urinary creatinine is excreted mainly by glomerular filtration with only small amounts via tubular secretion, serum creatinine and a 24-hour urine creatinine excretion are used to estimate GFR. Serum creatinine is increased in acute or chronic renal failure, urinary tract obstruction, reduced renal blood flow, shock, dehydration, and rhabdomyolysis. Causes for low serum creatinine concentration include debilitation and decreased muscle mass. Exercise may cause an increased creatinine clearance. If urine flow is low, creatinine clearance rate is unreliable.

**Biomarkers of AKI**

Because creatinine and BUN are flawed, better measures of function have been sought. Cystatin C, a proteinase inhibitor synthesized and released at a nearly constant rate by all nucleated cells, is an attractive option. This compound is filtered by the glomerulus and is completely metabolized by the proximal renal tubule without secretion or reabsorption. Hence, increases in serum levels correlate well with declines in GFR. In addition, the rise in serum cystatin C after kidney injury may precede increases in serum creatinine by 1 to 2 days, providing an early marker of injury. Use of cystatin C alone or in combination with creatinine strengthens the association between estimated GFR and the risks of death and end-stage renal disease. This association has been confirmed across diverse populations.

In addition to cystatin C, several other biomarkers have been evaluated. Three of these markers, interleukin 18 (IL-18), kidney injury molecule 1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL) have been investigated. After a renal insult, all three markers have been identified in serum well before creatinine or BUN become abnormal.

Multicenter studies of most biomarkers have not been conducted. It is likely that no single indicator will be able to reliably predict early AKI as well as severity and duration of renal dysfunction in all clinical settings. For example, the pathophysiology of ischemia-reperfusion-related kidney injury is different from that of sepsis-associated and radiocontrast-induced injuries. Each of these clinical entities may best be detected by a different set of indicators at different clinical time points. Biomarkers are being investigated for their ability to complement rather than
replace creatinine. In addition, the ability of an index to detect acute changes in kidney function may be affected by pre-existing chronic kidney disease.

DEFINITIONS OF ACUTE KIDNEY INJURY

Innumerable definitions of “renal failure” have been used causing difficulty interpreting the literature of this field. Traditionally, a rise in creatinine of 0.5 mg/dL or a doubling of creatinine (or halving of calculated GFR) has been considered clinically significant. Oliguria has been defined variably as urine production less than 400 mL/d or less than 0.5 mL/kg/h. The mortality of oliguric renal failure is at least twofold greater than nonoliguric failure, and for survivors, time to recover function is shorter among nonoliguric patients. Reasons for these observations are uncertain but probably reflect differences in severity of AKI and perhaps etiology. Unfortunately, little data suggest that “converting” oliguric to nonoliguric renal failure using diuretics alters outcome.

In the last few years, the development of a standardized staging system, RIFLE, has been useful. The RIFLE system (Table 29-2) uses calculated GFR and urine output to classify patients along a continuum of risk, injury, or failure and then finetunes the duration of failure as either persistent loss (>4 weeks) or end-stage disease (>3 months). The poorest performing metric defines the level of injury; thus, if serum creatinine places the patient in the “at-risk” category and urine output places the patient in the “injury” category, the patient would be classified in the latter. The system has been validated in a variety of critically ill populations. Recent data suggest that perhaps even smaller changes in creatinine (0.3 mg/dL) than those of the RIFLE risk group are associated with an increased length of stay, need for RRT, and risk of death.

Modification of the RIFLE criteria was proposed by an international collaboration of nephrologists and intensivists, which produced AKIN. This proposal included renaming the stages of AKI with numerical values and including an absolute serum creatinine elevation of 0.3 mg/dL over baseline as a qualification for placement into the “risk” category. A third and more recent consensus-approved definition schema, KDIGO, is intended to address shortcomings of the first two scoring systems by defining AKI as any of the following: increase in serum creatinine by greater than or equal to 0.3 mg/dL within 48 hours, increase in serum creatinine to greater than or equal to 1.5 times baseline that is known or presumed to have occurred within the prior 7 days, or urine volume less than 0.5 mL/kg/h for 6 hours.

Table 29-2. Criteria for Acute Kidney Injury

<table>
<thead>
<tr>
<th>RIFLE Criteria for Acute Kidney Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine, GFR Criteria</td>
</tr>
<tr>
<td>Risk</td>
</tr>
<tr>
<td>Increased SCreat × 1.5 or GFR decrease &gt;25%</td>
</tr>
<tr>
<td>Injury</td>
</tr>
<tr>
<td>Increased SCreat × 2 or GFR decrease &gt;50%</td>
</tr>
<tr>
<td>Failure</td>
</tr>
<tr>
<td>Increase SCreat × 3 GFR decrease 75% or SCreat ≥4 mg/dL</td>
</tr>
</tbody>
</table>
ETIOLOGY OF ACUTE KIDNEY INJURY

Approximately, 20% of critically ill patients develop AKI—an incidence five times that of the general hospital population. The risk of developing AKI is highest among patients who have underlying renal impairment. Roughly, 25% of these patients or 5% of all ICU residents will receive RRT. The etiology of AKI differs
drastically, depending on whether the condition develops in or outside the hospital and varies with the chronicity of the process. For example, poorly controlled hypertension and diabetes mellitus are the most common etiologies of slowly developing renal failure outside the hospital. When AKI develops outside the hospital, glomerulonephritis (GN), vasculitis, and obstructive uropathy are common causes. By contrast, AKI developing in the hospital is much more likely to be the result of hypoperfusion or drug toxicity—often now on a background of mild chronic renal dysfunction.

AKI may result from a variety of causes acting through one of three common mechanisms: (1) hypoperfusion (prerenal), (2) outlet obstruction (postrenal), or (3) parenchymal disease (intrarenal) (Fig. 29-1).

**Prerenal Failure**

Hypoperfusion accounts for half of all cases of AKI; hence, prevention of hypotension or its rapid reversal is probably the most effective therapy. Although prolonged ischemia alone may lead to AKI, in most cases, the etiology is multifactorial (i.e., severe sepsis, drugs, and hypotension). In general, mean arterial pressures less than 60 to 70 mm Hg are accompanied by a risk of injury, particularly if there is accompanying hypoxia. Hypoperfusion results from circulatory failure, hypotension, vascular obstruction (e.g., renal artery stenosis, vasculitis, embolization of bland clot or cholesterol, or maldistribution of cardiac output [CO], as in severe sepsis). The hepatorenal syndrome (see Chapter 31) and the renal response to positive end-expiratory pressure (PEEP) mimic prerenal physiology by redistributing blood flow away from the filtering glomerulus.
Marked increases in intra-abdominal pressure (abdominal compartment syndrome), usually greater than 20 mm Hg, resulting from the accumulation of ascitic fluid or blood, can also produce a prerenal state. It is uncertain if elevated abdominal pressures lessen urine flow by reducing CO through impaired venous return, by obstructing kidney arterial supply or venous outflow, or by compressing the kidney parenchyma directly. It appears unlikely that ureteral obstruction is etiologic because placement of ureteral stents does not improve flow. Regardless of mechanism, when elevated pressures are responsible for oliguria, decompressive laparotomy or paracentesis is generally associated with restoration of urine flow.

**Indicators of Intravascular Volume Status**

Orthostatic blood pressure is a helpful clinical measure of intravascular volume status in healthy persons. However, few critically ill patients can be tested in this fashion, and autonomic insufficiency renders such changes less reliable in patients who are diabetic, elderly, or bedridden. Dry mucous membranes, skin laxity, and absence of axillary moisture may also be clues to hypovolemia. Unfortunately, these signs, too, prove unreliable.
in patients with hyperpnea or advanced age. For the hospitalized patient, a persistently negative fluid balance supports a prerenal diagnosis.

Response to fluid challenge is the diagnostic hallmark of prerenal disease. The rate and volume of fluid administered must be customized taking into account the estimated magnitude of the deficit and cardiopulmonary reserves. Repeated boluses of 15 to 20 mL/kg are typically administered until deemed futile or function improves. Because noninvasive methods to assess fluid status (chest radiograph and echocardiogram) are insensitive tests of intravascular depletion, invasive monitoring is often undertaken (see Chapter 2). The need for invasive monitoring is controversial, however, because no

particular values for central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), CO, or systemic vascular resistance (SVR) guarantee sufficient or inadequate renal blood flow. That is, glomerular pressure and flow are poorly gauged by these hemodynamic measures. Nevertheless, a low intravascular pressure (i.e., CVP ≤ 2 or PAOP ≤ 5 mm Hg) can be diagnostically helpful, especially if CO is reduced concomitantly.

In prerenal failure, initially the urinalysis is normal or minimally abnormal with hyaline casts and other nonspecific sediment; however, if the injury is sufficient to induce tubular damage, typical ATN sediment will be present. A prerenal state prompts the tubule to reabsorb Na\(^+\) and water, yielding concentrated urine with low Na\(^+\). A urine Na\(^+\) less than 20 mEq/L, urine osmolality greater than 500 mOsm/L, and the urine specific gravity greater than 1.015 are typical. The fractional excretion of sodium (FENa) is another commonly used index to identify the prerenal state that measures the percentage of filtered sodium that is excreted. FENa is calculated as the ratio of the urine Na\(^+\) concentration times the plasma creatinine concentration to the product of the plasma Na\(^+\) concentration times the urine creatinine concentration:

\[ \text{FENa} = \left( \frac{\text{Urine Na}^+ \times \text{Plasma creatinine}}{\text{Plasma Na}^+ \times \text{Urine creatinine}} \right) \times 100 \]

FENa values less than 1% are generally indicative of prerenal disease, whereas values greater than 3% usually represent acute tubular necrosis (ATN). Intermediate values are not helpful and there are exceptions to this rule. For example, up to 10% of cases of ATN have a low FENa. For urine Na\(^+\) or FENa measurements to be valid, the underlying Na\(^+\) reabsorbing capacity of the renal tubule must be intact. For this reason, chronic renal failure, hypoaldosteronism, and metabolic alkalosis may all render tests of urine Na\(^+\) invalid. Likewise, diuretic therapy invalidates urine Na\(^+\) determinations for at least 24 hours. Osmotic agents (glucose, mannitol, radiographic contrast) also confuse interpretation of urine chemistry values by diluting the urine. Cutoff values of less than 1 and greater than 3 for FENa are relevant only in the context of significant AKI or severely reduced GFR.

Table 29-3. Kidney Size as a Clue to the Etiology of Renal Failure

<table>
<thead>
<tr>
<th>Normal</th>
<th>Enlarged</th>
<th>Small</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute glomerulonephritis</td>
<td>Amyloidosis, Sarcoid, Lymphoma</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Radiograph exposure</td>
<td>Acute glomerulonephritis</td>
<td>Chronic hypertension</td>
</tr>
<tr>
<td>Acute cortical necrosis</td>
<td>Acute interstitial nephritis</td>
<td></td>
</tr>
<tr>
<td>Acute interstitial nephritis</td>
<td>Obstructive uropathy</td>
<td></td>
</tr>
</tbody>
</table>
Although the BUN may be disproportionately high because of increased urea production resulting from insults such as tetracycline, corticosteroids, or GI bleeding, an elevated BUN/creatinine ratio more commonly results from reduced tubular urine flow and increased proximal tubular reabsorption of urea nitrogen. Thus, in prerenal states, the BUN/creatinine ratio is usually elevated (>10:1; sometimes >20:1). Because the renal tubules cannot absorb creatinine, reduced tubular flow rates have no effect on the creatinine concentration if GFR is preserved. Comparing urea clearance to creatinine clearance will determine whether increased urea production or decreased urea excretion is the cause of an elevated BUN. If the urea/creatinine clearance ratio is greater than 1, increased production is the likely etiology. The most common clinical task is to differentiate prerenal disease from ATN. Table 29-1 compares the more common renal function indicators in these two conditions. Imaging studies of the kidneys may also provide clues to the cause of renal failure (Table 29-3). In most forms of AKI, the kidneys will be of normal size when imaged with ultrasound or computed tomography (CT). Small kidneys suggest a more chronic process (e.g., diabetes or hypertension) with a superimposed insult.

**Postrenal Failure**

Once prerenal causes have been excluded, obstructive or postrenal causes (e.g., urinary calculi or clots, tumor, prostatic hypertrophy, retroperitoneal hemorrhage) should be considered. Even though obstructive disease accounts for less than 10% of cases of AKI, this reversible problem cannot be overlooked. Because of the low risk and cost, practically every patient developing AKI should have an imaging study to exclude obstruction. The pattern of decline in urine flow can provide a valuable clue to the presence of obstructive disease. In both prerenal and intrarenal failure, the development of oliguria or anuria is usually gradual over hours to days, whereas an abrupt cessation of flow often occurs with obstructive uropathy. (Urethral obstruction by prostatic enlargement, trauma, or blood clot is the most common cause of anuria.) In catheterized patients, a clogged or dysfunctional catheter is a common cause for sudden “anuria,” in which case flushing the catheter is diagnostic and therapeutic. Upper tract obstruction produces anuria only if bilateral or if it occurs in a patient with a single kidney or drainage pathway. In this setting, tumor (e.g., bladder, kidney, prostatic, or ovarian), stone, and clot are the most common etiologies. Urethral obstruction may be immediately excluded or confirmed by the attempt to place a catheter into the bladder. Because of the high incidence of urinary collecting system abnormalities, however, urinary bladder catheterization alone never excludes the possibility of more proximal obstructive uropathy. Renal ultrasonography and CT scan can detect hydronephrosis and urinary obstruction within or proximal to the bladder and have supplanted the outmoded intravenous pyelogram (IVP).

In obstructive uropathy, the urinalysis is usually normal, at least initially, and urine studies are seldom enlightening. A notable exception would be discovery of hematuria suggesting papillary necrosis or obstruction by stone, clot, or tumor.
Intrarenal Failure

The history, urinalysis, and urinary chemistry profile provide clues to distinguish prerenal from intrarenal causes of AKI (Tables 29-1 and 29-4). However, no single index of renal function yields a specific diagnosis in AKI. For example, although the FENa is usually greater than 1 when “intrarenal” failure occurs, diuretic use, glycosuria, mannitol, and prolonged urinary obstruction can produce identical findings. Similarly, the urinalysis can be very informative if it reveals red cell casts (vasculitis or GN), eosinophils (acute interstitial nephritis [AIN]), or crystals (ethylene glycol, uric acid nephropathy) but is rarely unequivocal. The size of the kidneys may also provide a useful clue to the etiology of renal failure. If the kidneys are small, then renal failure is at least in part chronic. By contrast, normal size or large kidneys are much more common in acute renal failure. Renal enlargement is indicative of a limited number of acute etiologies, including obstruction, renal vein thrombosis, and transplant rejection (see Table 29-3).

There are three major categories of acute intrarenal failure: (1) tubular disorders, (2) interstitial nephritis, and (3) GN and small vessel vasculitis.

Tubular Disorders

The most common form of AKI results from tubular injury commonly called ATN. ATN is not a unique entity and should be considered the severe extreme of the continuum of AKI induced by ischemia and drugs. ATN manifests clinically as an abnormal urinalysis featuring muddy brown and epithelial cell casts, a high urinary Na⁺ greater than 40 mEq/L, a FENa greater than 2%, and a urine osmolality less than 400 mOsm/L reflecting the loss of tubular concentrating ability.

<table>
<thead>
<tr>
<th>Urine Sediment</th>
<th>Associated Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red cell casts</td>
<td>Glomerulonephritis, vasculitis, trauma</td>
</tr>
<tr>
<td>Heme pigmented casts</td>
<td>Hemoglobinuria, myoglobinuria</td>
</tr>
<tr>
<td>Leukocyte casts</td>
<td>Pyelonephritis, papillary necrosis</td>
</tr>
<tr>
<td>Renal tubular casts</td>
<td>Acute tubular necrosis</td>
</tr>
<tr>
<td>“Muddy” granular casts</td>
<td>Acute tubular necrosis</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>Urinary infection, interstitial nephritis</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>Interstitial nephritis</td>
</tr>
<tr>
<td>Crystals</td>
<td>Urate, oxalate (ethylene glycol)</td>
</tr>
</tbody>
</table>

ATN is usually multifactorial in etiology, but drugs often play a role. Aminoglycosides, amphotericin, contrast
media, cyclosporine, platinum-based chemotherapeutic agents, angiotensin converting enzyme (ACE) inhibitors, and nonsteroidal antiinflammatory drugs (NSAIDs) are most commonly implicated. Elderly, dehydrated, hypertensive, and diabetic patients and those with mild underlying renal dysfunction and myeloma are at particular risk of drug-induced AKI. Aminoglycosides cause renal insufficiency in 10% to 20% of patients who receive them by binding and injuring cellular proteins in the proximal tubule. Damage is most likely with sustained elevated trough drug levels. (Peak levels correlate with bacterial killing, whereas trough levels predict toxicity.) Toxicity is potentiated by pre-existing renal disease, volume depletion, and concomitant use of other nephrotoxins. Because prolonged exposure of the renal tubule to drug and not peak levels appears to be the critical determinant of damage, dosing once daily (e.g., gentamicin 5 mg/kg) lowers the risk of nephrotoxicity. Such a dosing schedule is also more convenient and less costly. Because the duration of exposure is also a risk factor, limiting the length of therapy reduces risk. When using aminoglycosides, frequent mistakes are to administer multiple daily doses and to empirically treat for prolonged periods without a clear indication. Although aminoglycoside loading doses need no modification, maintenance doses should be reduced in proportion to GFR. (For example, a patient with 50% of predicted GFR should receive roughly 50% of the standard maintenance dose.) Serum trough levels should not be determined until after five half-lives when steady-state concentrations are achieved. Fortunately, aminoglycoside use has declined dramatically with the development of less-toxic alternatives, and almost all patients with aminoglycoside-induced AKI recover sufficient function to eliminate the need for long-term dialysis.

Radiographic contrast-induced nephropathy (CIN) is a rare cause of AKI in patients with normal baseline renal function but frequently produces AKI in patients with underlying volume depletion, renal disease, diabetes mellitus, or paraproteinemia. Fortunately, an isolated rise in creatinine is much more common than full-blown AKI requiring dialysis. Risk is higher among patients receiving hypertonic and ionic contrast agents and is proportional to the number of exposures and volume of contrast (highest with doses >2 mL/kg). Consequently, it makes sense to bundle together imaging studies requiring intravenous contrast to minimize exposure and select the contrast agent carefully in at-risk patients. Although not studied in large randomized trials, volume loading appears to be beneficial for prevention of CIN. For this purpose, current evidence suggests that isotonic fluids are superior to hypotonic fluids and that perhaps NaHCO₃ may be superior to NaCl. The mechanism of protection is unknown but probably involves a combination of volume expansion (enhanced tubular flow) and an antioxidant effect. If time for pretreatment is available, two to four doses of oral N-acetylcysteine (NAC) (600 mg q12h) may reduce the risk of CIN and is safe and inexpensive. Oral NAC regimens begin 24 to 48 hours before contrast exposure, limiting their usefulness in the emergent setting. Literature supporting this recommendation is inconsistent. Similarly, the effectiveness of immediate pretreatment with intravenous NAC is unclear. There is no role for prophylactic dialysis to remove contrast as toxicity related to contrast administration is mostly a first-pass effect causing vasoconstriction at the arteriole. Fluid volume passing through the afferent arteriole when dye is injected is the main determinant of AKI associated with contrast administration. There is no benefit in dialyzing to remove iodinated contrast as renal injury has already occurred. Gadolinium is one material which can be dialyzed off but in general is avoided entirely in high-risk patients.

NSAIDs may impair renal function in patients with prerenal azotemia, shock, heart failure, cirrhosis, and nephrotic syndrome. Prostaglandin E₂ (PGE₂), an endogenous vasodilator, is pivotal in maintaining renal blood flow in patients with high renin/angiotensin states. In such patients, NSAIDs can block PGE₂ formation, decreasing renal blood flow. Furthermore, NSAIDs encourage sodium, potassium, and fluid retention and inhibit diuretic action. If NSAIDs are used, aspirin is the best option. Despite concerns regarding chronic use, there is no evidence that short-term use of NSAIDs (COX2 or nonselective) in usual doses increases risk of cardiovascular death.

ACE inhibitors block formation of angiotensin II, thereby reducing systemic blood pressure
and dilating postglomerular arterioles. Both effects reduce glomerular perfusion pressure and may precipitate AKI when perfusion is marginal, especially among patients with bilateral renal artery stenosis or a single kidney. Beginning an ACE inhibitor in a critically ill patient with congestive heart failure and a concomitant creatinine elevation is often a difficult decision, especially if renal artery anatomy is not known. Fortunately, for most patients, the increased CO stemming from reduced afterload provides more benefit than any direct negative effect of the ACE inhibitor on renal blood flow. If renal function deteriorates, prompt discontinuation of the ACE inhibitor usually results in return of renal function to baseline. The combination of ACE inhibitors and NSAIDs is especially detrimental to renal function because of the synergistic effects on perfusion.

The cellular pigments, myoglobin, and hemoglobin may induce AKI when released into serum during hemolysis or rhabdomyolysis. Both myoglobin and hemoglobin precipitate in the renal tubules, obstructing them by forming pigmented tubular casts. Trauma, severe sepsis, seizures, statin toxicity, prolonged immobilization, and hyperthermic illnesses like neuroleptic malignant syndrome and heatstroke can all be etiologic. Half of all patients have no complaints of muscle pain, tenderness, or weakness. Clues to AKI associated with rhabdomyolysis include rapidly increasing creatinine with disproportionate rises in K⁺, PO₄³⁻, and uric acid. Volume loading with isotonic saline or bicarbonate, osmotic diuretics, and alkalinizing agents may help to keep these pigments in solution, thus encouraging their elimination and preventing AKI.

Among patients with lymphoid malignancies who have a high tumor burden, spontaneous tumor death or that from chemotherapy and/or radiation releases large quantities of uric acid, which can rapidly produce AKI. Patients with tumor lysis syndrome have rapidly increasing levels of released intracellular components K⁺ and PO₄³⁻ and a resulting fall in serum Ca²⁺. Use of the xanthine oxidase inhibitor, allopurinol, to stop uric acid formation, or a synthetic urate oxidase enzyme to degrade uric acid, is beneficial. Adequate hydration is a key prophylactic step but urinary alkalinization is probably not helpful.

**Interstitial Nephritis**

AIN is a common but frequently unrecognized immune-mediated tubulointerstitial injury. Infection and medications including penicillins, cephalosporins, sulfonamides, quinolones, rifampin, thiazides, furosemide, NSAIDs, allopurinol, and cimetidine are reported causes. AIN may present with fever, eosinophilia, and rash; however, oliguria and a rising creatinine are often the only indications. Laboratory clues to diagnosis include eosinophilia in about 1/4 of cases and eosinophiluria in about 2/3 of patients. Hansel stain is necessary to document urinary eosinophilia. (Wright stain is pH dependent and often fails to demonstrate eosinophils in the urine.) Removal of the suspect offending drug is indicated, and where medication causes this insult, steroids return renal function to normal over several weeks. Renal biopsy is sometimes needed to make this diagnosis.

**Glomerulonephritis and Vasculitis**

Although GN and vasculitis represent relatively common etiologies for AKI developing outside the hospital, they are uncommon causes of abrupt renal failure in the ICU. The diverse spectrum of these disorders includes poststreptococcal GN, rickettsial infection, subacute bacterial endocarditis, systemic lupus erythematosus (SLE), malignant hypertension, and drug-related vasculitis. Urinalysis reveals sediment containing leukocytes, protein, and the hallmark of GN, red blood cell (RBC) casts. Specific diagnosis may be aided by measurement of serum complement, antinuclear cytoplasmic antibodies (ANCA) and antinuclear antibody (ANA) studies, rheumatoid factor, hepatitis B surface antigen, and blood culture. Therapy is directed at the underlying condition (e.g., antibiotics for infection including endocarditis, steroids for SLE, and cytotoxic therapy for Wegener granulomatosis and polyarteritis).

**COMPLICATIONS AND TREATMENT OF ACUTE RENAL FAILURE**
Prevention

Because the only therapy after AKI that is established is supportive, it is clear that the best treatment is prevention. Avoiding hypotension and hypoxia and recognizing urinary obstruction can prevent the majority of cases of AKI. Parsimonious use of nephrotoxic drugs in appropriate doses is the next most important preventative measure. Volume expansion with isotonic saline or sodium bicarbonate is probably the most effective prophylaxis against AKI induced by contrast agents, rhabdomyolysis, cis-platinum, methotrexate, or cyclophosphamide.

Established Oliguric Renal Failure

Prolonged illness before admission and delays in transferring patients from the general care floor or another hospital often postpone the diagnosis of oliguric AKI until 12 to 48 hours after its onset. Even if evaluation is delayed, it is prudent to exclude obstructive uropathy. When presented with a patient with established oliguric AKI, several measures should be undertaken to prevent additional injury and perhaps forestall or avert the need for dialysis or hemofiltration (HF). First, all nonessential nephrotoxins should be discontinued, and any necessary drug cleared by the kidney should have its dose modified based on the assumption of a zero GFR. Second, limit fluid intake by discontinuing “maintenance fluids” and unnecessary drugs, and concentrating the required drugs makes common sense. Next, because $K^+$ and $PO_4^{3-}$ levels rise as the result of normal metabolism, intake of $K^+$ and $PO_4^{3-}$ should be minimized unless the patient exhibits significant symptomatic hypokalemia or hypophosphatemia. (Do not forget to modify the diet.) If $PO_4^{3-}$ levels are already elevated, it makes sense to begin oral $PO_4^{3-}$ binders in patients who are eating. Likewise, if the patient is hyperkalemic, oral or rectal K binding resin should be considered. Rectal potassium binding agents are controversial because of risk of colonic necrosis. Potassium binding resins exchange $Na^+$ for $K^+$ and can contribute to volume overload. Acute and symptomatic hyperkalemia is addressed with administration of intravenous calcium gluconate, insulin, and glucose. In this setting, calcium helps to stabilize the myocardium, while insulin shifts potassium into the cells and glucose prevents hypoglycemia associated with insulin administration. Mg supplements should be discontinued to avoid exceeding the limited excretory capacity. Providing $HCO_3^-$ enterally can blunt the development of acidemia. Finally, it is wise to involve a nephrologist early in the care of the patient. Not only can they provide valuable advice, but it is also simple courtesy to inform them about potential dialysis candidates so that they may best schedule any required intervention.

Table 29-5. Complications of Acute Kidney Injury

<table>
<thead>
<tr>
<th>Metabolic</th>
<th>Cardiovascular</th>
<th>Neurologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>Fluid overload</td>
<td>Neuropathy</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Hypertension</td>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Arrhythmias</td>
<td>Seizures</td>
</tr>
</tbody>
</table>
Early Oliguric Renal Failure

For patients seen shortly after developing oliguria, the initial approach should be to eliminate prerenal factors, exclude obstructive uropathy, and, when possible, reverse oliguria. After prerenal and postrenal causes have been excluded, careful review of the history, physical examination, and laboratory and medication records may give clues to the cause. Unfortunately, AKI often occurs in the setting of multiorgan failure where potential etiologies are numerous. In this situation, combined renal and respiratory insufficiency is ominous. Interestingly, even with appropriate dialysis, morbidity and mortality remain high as a result of nonrenal causes (Table 29-5). In patients with acute renal failure, supportive care must be meticulous to maximize chances for survival. It is most important to avoid such iatrogenic complications as infection related to monitoring devices, fluid and electrolyte imbalances, drug toxicity, and inappropriate nutritional support.

Hemodynamic Management

Nonoliguric AKI is associated with lower mortality than the oliguric variety. Unfortunately, this fact is often misinterpreted. A response to measures designed to restore urine flow is not necessarily an indication of improved renal function but may simply serve as an indicator of a patient's overall physiologic condition and the severity of the underlying injury. Perhaps responders have better baseline renal function or more cardiovascular reserve than nonresponders. Although it is not proved that restoring urine flow reduces mortality, attempting to restore flow is still probably worthwhile because it vastly simplifies fluid management.

When attempting to reverse oliguria, a fluid challenge of 15 to 30 mL/kg of isotonic crystalloid should be performed first unless there are obvious signs of intravascular congestion. Invasive monitoring can be considered in patients with tenuous cardiopulmonary reserve and when volume status is particularly difficult to assess (e.g., edema, hypoproteinemia). The limitations of invasive monitoring catheter must be recognized; no combination of measurements guarantees adequate glomerular flow. (Nevertheless, a low CVP, PAOP, and CO with increased SVR suggest that more fluid may be beneficial.) Next, a single sizeable dose of loop diuretic (e.g., furosemide, 1 mg/kg) can be tried, but it makes little sense to continue diuretics in established oliguria, and observational studies suggest possible harm from continued use. Although single doses of osmotic diuretic (mannitol, 25 to 50 g) may also be effective, any potential benefit needs to be balanced against the risk of volume overload and hyperosmolarity. Measures to reverse the oliguric state are most likely to be successful when undertaken shortly after the reduction in urine flow. When 8 or more hours have elapsed, efforts to restore urine flow by volume loading are more likely to fail.
Once assured that intravascular volume is adequate, vasoactive drug therapy may be helpful in the hypotensive acutely oliguric patient. Any drug that raises mean arterial pressure to 60 to 65 mm Hg is likely to boost urine output. There are no data to indicate superiority of one vasopressor over another, and currently, norepinephrine is used most commonly. Historically, “low-dose” dopamine was often chosen as a first-line agent because of its ability to increase CO through β-adrenergic receptor stimulation and increase renal blood flow via dopaminergic receptor stimulation. It is now clear that low-dose dopamine does not prevent the development, alter progression, or hasten recovery of AKI. Although it is perfectly fine to use dopamine for its vasoactive properties, there is no beneficial effect associated with doses that do not boost perfusion pressure.

**Electrolyte Disorders**

Hyperkalemia, hyponatremia, hypermagnesemia, and hyperphosphatemia are the major electrolyte disturbances of AKI. The primary approach to each disorder is to modify input and/or enhance removal of solute or fluid, as detailed in Fluids and Electrolyte Disorders, Chapter 13. Because Mg\(^{2+}\) excretion is impaired in patients with AKI, Mg\(^{2+}\)-containing products (antacids and cathartics) should be avoided. Phosphorous-containing enemas are also avoided because of risk of acute phosphate nephropathy.

Water, Na\(^+\), and K\(^+\) intake should be adjusted to match measured urinary output and normalize serum values. In the resolution phase of ATN (variable onset and duration), patients frequently undergo a polyuric period during which fluid losses may be associated with significant morbidity unless appropriately replaced. The cause of the polyuric phase is not known with certainty but probably results from tubular dysfunction in the face of recovering GFR and excess total body water.

**Infection**

Infection-induced multiple organ failure is arguably the most common cause of death in acute renal failure. With the possible exception of pyocystis, a pusfilled nondraining bladder, the infections acquired by patients with AKI do not differ from those of other ICU patients. In decreasing frequency, nosocomial pneumonia and IV catheter-related infections lead the list. Among patients dying with renal failure, however, there may be a disproportionate occurrence of intra-abdominal sepsis. The clues to suspect infection and the techniques to diagnose and treat various infections are outlined in Chapter 26.

**Bleeding Disorders**

Hemorrhage (primarily GI) accounts for a substantial number of deaths among patients with AKI. Bleeding is common because of the inhibitory actions of uremic toxins on platelets and factor VIII. The key to reversing coagulation disorders is to improve the environment in which the platelets and clotting factors function. Most commonly, this is accomplished through adequate dialysis. Replacement of factor VIII with purified concentrates, cryoprecipitate, or fresh frozen plasma (FFP) may transiently help to correct bleeding defects (see Chapters 14 and 30). Likewise, arginine vasopressin (DDAVP) will temporarily improve hemostasis in uremic patients by increasing levels of factor VIII complex. (Unfortunately, tachyphylaxis is seen within just one or two doses.) Platelet transfusions may also briefly improve hemostasis before invasive procedures.

**Nutrition**

The production of uremic toxins can be reduced by minimizing catabolism and providing sufficient calories to prevent protein wasting. Except in AIN and some forms of renal vasculitis, corticosteroids should be avoided because of their catabolic effects and impact on immune function. For most AKI victims, caloric requirements...
generally range from 2,500 to 3,000 calories per day. Sufficient carbohydrate (>100 g/d) and fat calories should be provided to prevent the catabolism of protein for energy production. Limitation of protein intake in patients with renal insufficiency is unnecessary and probably inappropriate. In general, patients should be given sufficient protein to optimally support them through critical illness. In circumstances where products of protein metabolism accumulate, RRT should be considered rather than reducing intake of a key metabolic substrate. Folate and pyridoxine must be supplemented because they are lost through HD. If total parenteral nutrition (TPN) is used, a formulation low in Na\(^+\), Mg\(^{2+}\), PO\(_4^{3-}\), and K\(^+\) is mandatory. Enteral feeding is preferred because of the lower fluid volume, infection risk, and costs.

**Drug Therapy**

The need for every medication should be questioned in AKI. Any drug that may impair renal function should be discontinued or its dosage appropriately modified. Renally metabolized or excreted drugs require dose modification. As a general guideline, the dosage needs revision in proportion to its percentage of elimination by the kidney and the degree of renal impairment. Dosing of each drug susceptible to renal excretion should be guided by published nomograms. Even when dosage is precisely calculated, it is probably prudent to follow levels of drugs with a low therapeutic index.

**Renal Replacement Therapy**

**Indications**

Indications for HD or HF are (1) fluid overload, (2) refractory hyperkalemia or hypermagnesemia, (3) life-threatening metabolic acidosis, (4) symptomatic uremia (e.g., pericarditis, seizures, encephalopathy), and (5) presence of a dialyzable toxin (salicylate, methanol, ethylene glycol). Peritoneal dialysis may be considered in selected cases of chronic renal insufficiency but is seldom applicable in the acute care setting.

**Overview of Methods**

The terminology surrounding RRT is confusing, but each technique is derived from three basic characteristics: (1) the method used to remove the solutes (diffusion, convection, or a combination), (2) whether the process is intermittent or continuous, and (3) the access site (arteriovenous or venovenous). Two basic methods of fluid and solute removal can be used: hemofiltration, a process in which fluid and the solutes it contains are removed from blood by convection, (a hydrostatic pressure gradient moves solute-containing fluid across a semipermeable membrane), and HD (solutes diffuse down a concentration gradient). These techniques are frequently combined as **hemodiafiltration**, a system combining diffusion and convection to remove fluid and solute from blood (Fig. 29-2).

Access to the circulation is achieved by inserting either a multilumen venous catheter or one arterial catheter for supply and one venous catheter for blood return. Jugular and femoral venous sites are acceptable. When an artery is used, it is almost always a femoral vessel, necessitating that the patient remains supine. Venovenous access is usually preferred because only one catheter is needed and it avoids risks of limb ischemia from artery occlusion by the catheter itself, clot, or cholesterol embolism. Avoiding arterial access also precludes arterial air embolism and permits less-intense anticoagulation. Because arteriovenous methods usually use the patient’s blood pressure to power flow through the circuit, problems of low flow in patients with hypotension or peripheral arterial disease occur frequently. The more commonly used venovenous filtration overcomes this problem by introducing an
extracorporeal pump. The higher blood flows (≥200 mL/min) through this apparatus compensate for the “recirculation” that occurs through the adjacent ports. Because of their comparatively rigid construction and large diameter, dialysis catheters are more prone to perforate vascular structures during insertion and erode through vessel walls over time than conventional venous access catheters. Particular care should be used during insertion, making sure that the catheter advances easily over the guidewire. If inserted in the neck or thorax, a radiograph should be obtained to confirm that the catheter tip is aligned with the luminal axis and does not terminate in the heart.

FIGURE 29-2. Hemofiltration versus hemodialysis. See text for details.

Because flow rates and solute clearance achieved by HF alone are lower, this process is typically done continuously. In contrast, the higher flow rates and solute clearance of HD permit intermittent sessions. A summary of the characteristics of various blood purification methods is provided in Table 29-6. Of the modalities described, intermittent hemodialysis (IHD) and sustained low-efficiency dialysis (SLED) represent pure diffusion techniques with IHD a more aggressive approach than SLED. The remaining four modalities are typically done at the bedside over extended periods of time and are better utilized in the critically ill patient at risk for hemodynamic instability.

**Hemofiltration**

HF is the removal of solute-containing fluid by convection across a semipermeable membrane. HF can be accomplished using an extracorporeal pump to power the flow of venous blood or by using the patient's arteriovenous pressure gradient to drive flow through a hollow fiber cartridge (often called a “dialyzer”).
Typically, non-pump-aided filtration becomes ineffective when mean arterial pressure is less than 60 mm Hg; thus, a pump is generally used. The filtration rate can be increased by restricting cartridge outflow (raising downstream venous pressure), by increasing the cartridge inflow pressure (either arterial pressure or pump pressure), or by increasing blood flow rate or the transmembrane filtration pressure by applying suction to the shell surrounding the permeable fibers. (Obviously, increasing the cartridge surface area will also boost filtration rate.) Conversely, filtration may be decreased by restricting blood inflow or pump supply pressure.

In its simplest form, HF removes solutes in exactly the concentrations in which they are present in blood, as they are passively carried across the cartridge's semipermeable membrane in the plasma extract. Decreases in plasma urea or creatinine concentrations result by replacing the extracted ultrafiltrate with a nonurea-/creatinine-containing electrolyte solution, in essence diluting the plasma. As a result, changes in solute concentrations are slow. Although not at first obvious, infusing the replacement fluid upstream of the cartridge can increase urea clearance by diluting plasma concentrations, which encourages movement of urea from the freely permeable red cells into plasma.

HF, HD, or a combination of both techniques may be applied as continuous or intermittent therapy. See details of various modalities in Table 29-6. In general, targeted clearance rate for delivered therapy is 25 mL/kg/h.

Continuous therapies have several advantages over intermittent therapy. One advantage is the ability to be safely conducted by a critical care nurse in the ICU. Another major benefit of continuous therapy is that is much less likely to result in hypotension or cerebral edema than intermittent therapy, in part, because of slower changes in plasma osmolality. The continuous nature of filtration tends to reduce body temperature, which may raise blood pressure by increasing SVR. For these reasons, continuous therapy has become a favorite technique to treat the hemodynamically unstable patient. The relative inefficiency of solute clearance is offset by continuous application. Even though solute clearance rates are generally low, rapid fluid removal rates (1 to 3 L/h) are possible with continuous therapy.

<table>
<thead>
<tr>
<th></th>
<th>IHD</th>
<th>SLED</th>
<th>SCUF</th>
<th>CVVH</th>
<th>CVVHD</th>
<th>CVVHDF</th>
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</thead>
<tbody>
<tr>
<td>Blood Flow (mL/min)</td>
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<td>0</td>
<td>17-34</td>
<td>17-34</td>
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<tr>
<td>Filtrate (L/d)</td>
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<td>0-4</td>
<td>0-4</td>
<td>48-96</td>
<td>0</td>
<td>24-48</td>
</tr>
<tr>
<td>Replacement Fluid (L/d)</td>
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<td>0</td>
<td>0</td>
<td>46-94</td>
<td>0</td>
<td>23-44</td>
</tr>
<tr>
<td>Effluent Saturation (%)</td>
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<tr>
<td>Solute Clearance</td>
<td>Diffusion</td>
<td>Diffusion</td>
<td>Convection</td>
<td>Convection</td>
<td>Diffusion</td>
<td>Both</td>
</tr>
</tbody>
</table>
In the absence of a blood pump, arteriovenous circuits can be used to provide continuous therapy (CAVH, CAVHD, CAVHDF). CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; IHD, intermittent hemodialysis; RRT, renal replacement therapy; SCUF, slow continuous ultrafiltration; SLED, sustained low efficiency dialysis. From Irwin RS, Lilly CM, Mayo PH, Rippe JM. *Irwin & Rippe’s Intensive Care Medicine*. 8th ed. Philadelphia: Wolters Kluwer; 2018: p. 1978.

The major disadvantages of continuous therapy are the requirement for anticoagulation, cost, and the amount of labor required. Continuous therapy usually requires a 1:1 nurse-to-patient assignment because each day 10 to 20 L of ultrafiltrate must be discarded and replaced using an appropriate volume of electrolyte solution. Without careful monitoring of output, patients are prone to volume depletion. Unless blood flow rates are high, anticoagulation may be required, and, in some cases, the anticoagulant effect may become systemic. Of available anticoagulant strategies, citrate provides the best regional effect. Heparin and argatroban are alternatives. Cartridge clotting may occur despite the use of anticoagulation. In addition, regardless of physician preferences, no compelling data indicate a survival advantage of continuous over intermittent therapy for patients who can tolerate the latter.

**Hemodialysis**

HD differs from HF because of the dialytic fluid on the opposite side of the semipermeable membrane from the blood. As a result, solutes not only filter from blood across the membrane governed by pore size but also diffuse down a concentration gradient as the dialysate is continuously exchanged using countercurrent flow. It is by combining convection and diffusion that HD achieves high solute clearance rates. Because the membrane is permeable in both directions, electrolytes in the dialysate equilibrate with those in plasma. Hence, the electrolytic composition of the dialysis fluid should roughly approximate desired plasma electrolyte concentrations. Backfiltration of dialysate into the patient necessitates sterility. By altering the pressure of blood on one side of the dialysis membrane and the pressure of the dialysate on the other, the amount of fluid filtered during HD can be precisely controlled. (Increasing the transmembrane gradient results in greater fluid losses.) HD machines can be used for HF by eliminating dialysate infusion and using the outflow port to drain the plasma ultrafiltrate.

Although more efficient than HF, HD requires cardiovascular stability; rapid shifts of fluid between intracellular and extracellular compartments induced by changes in osmolality are not well tolerated by hemodynamically unstable patients. Hypotension during HD is the most common significant problem. Fluid and electrolyte shifts, reactions to the dialysis membrane or dialysate, and impaired cardiac performance all play a part. (Hypotensive episodes generally result from rapid volume removal.) When this happens, water moves from the hypotonic plasma into cells, resulting in intravascular volume contraction and cellular edema. (Interestingly, HF has the opposite effect on cellular hydration; as water is filtered, plasma protein concentrations rise, leading to a net flux of water from cells into the plasma.) Another mechanism of hypotension is excessively rapid filtration reducing preload. Intravascular volume deficits respond quickly to crystalloid or colloid replacement and low-dose vasopressor support. If transfusion is planned, administration of blood during HD helps to minimize hypotension. If hypotension recurs with each dialysis session or occurs after only small volumes of fluid have been removed, a reaction to the dialysis membrane or to acetate in the dialysis bath should be considered. Fortunately, improvements in material technology have made this problem rare. Intolerance to HD is more common early in
the treatment course.

During HD, intraneuronal tonicity may not track the abrupt shifts in fluid/solute composition that occur in the extracellular compartment, producing the “dialysis disequilibrium” syndrome. Nausea, vomiting, confusion, seizures, and coma, all manifestations of the syndrome, occur most commonly in patients with high BUN concentrations undergoing initial dialysis. Disequilibrium can be minimized by using brief dialysis sessions, lower flow rates, and a small surface area cartridge. Administration of osmotically active compounds (NaCl, mannitol, or dextrose) can also reduce the frequency and severity of the syndrome.

Depending on the choice of membrane and dialysate, hypoxemia during HD may result from leukostasis within the pulmonary capillaries (cuprophane membrane) or from hypoventilation (acetate buffer). Hypoventilation occurs as CO₂ diffuses into the dialysate, reducing the stimulation of ventilatory chemoreceptors.

Using a naming convention identical to HF, HD is termed intermittent or continuous and venovenous or arteriovenous, depending on circulatory access. The term SLED, slow low-efficiency dialysis, is associated with long or continuous dialysis using lower blood flow and dialysate rates. The term hemodiafiltration is used to describe the process of HD with net filtration of fluid.

A variety of CRRT configurations exist. In SCUF (slow continuous ultrafiltration), ultrafiltrate is generated by the transmembrane pressure gradient produced by the blood pump. CVH (continuous venovenous hemofiltration), on the other hand, utilizes large volume ultrafiltrate with replacement fluid infused by a preblood pump, prehemofilter, or posthemofilter. A third modality is CVHD (continuous venovenous HD). Dialysate is pumped through the filter to generate diffusive solute clearance. Finally, a fourth CRRT configuration is CWHDF (continuous venovenous hemodiafiltration). These systems utilize high ultrafiltration with replacement fluid as well as dialysate (Fig. 29-3).

**Timing and Intensity of RRT**

Strong opinion exists with regard to optimal intensity and timing for initiation of RRT. Because uremia exerts globally negative metabolic effects, it makes sense to begin RRT as soon as it is clear that intervention will be needed and to provide sufficient support to normalize blood chemistry values. Retrospective and nonrandomized studies support earlier and more intense treatment by demonstrating improved survival and functional recovery, but these findings have not been corroborated by prospective randomized studies. In what may be the definitive study of dialysis intensity in which patients could cross over between intermittent and continuous methods of support, no difference between an intense and conventional RRT strategy was found. Hence, current information suggests that for most patients with AKI, the outcomes of thrice weekly intermittent HD sessions are equal to daily intermittent HD or continuous RRT support. An important exception to this rule is hemodynamically unstable or tenuous patients where CRRT is safer. CRRT may also decrease the likelihood of progression to long-term dialysis therapy. Another exception would be where toxin removal (ethylene glycol, methanol, lithium) is the goal in which case intense continuous RRT is often continued until the toxin is undetectable.
FIGURE 29-3. Diagram of various CRRT configurations. SCUF: Ultrafiltrate is generated by the transmembrane pressure gradient produced by the blood pump. CVVH: Large volume ultrafiltrate is generated, and replacement fluid is infused preblood pump, prehemofilter, or posthemofilter. CVVHD: Dialysate is pumped through the filter to generate diffusive solute clearance. CVVHDF: The system utilizes high ultrafiltration with replacement fluid as well as dialysate. CCRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; SCUF, slow continuous ultrafiltration. (From Irwin RS, Lilly CM, Mayo PH, Rippe JM. Irwin & Rippe’s Intensive Care Medicine. 8th ed. Philadelphia: Wolters Kluwer; 2018: p. 1978.)

PROGNOSIS
The survival of patients with AKI is more determined by the underlying conditions precipitating renal failure than by renal dysfunction itself. Attributed mortality relative to AKI has been reported at 5% to 10%. Rarely do patients die from renal failure if RRT is instituted. Recent data indicate that among patients who do not succumb to their underlying illness, recovery of
function is common. Nonetheless, functional recovery is much less likely for patients with chronic renal dysfunction before superimposed acute injury. Studies debate whether the need for RRT increases the likelihood of death in critically ill patients. Obviously, there are many confounders, which can affect this work.

Epidemiologic studies estimate that mortality rates in the period after RRT is initiated average 50% to 70%. Approximately 10% to 30% of patients who receive RRT in the hospital will need continued RRT after discharge.

**SUGGESTED READINGS**


• Key Points

1. Prothrombin time, an activated partial thromboplastin time, and a platelet count done after a careful, detailed history, which includes a review of current medications, can detect most of the acquired bleeding disorders seen in the ICU.

2. Coagulation tests are often indiscriminately performed. The activated partial thromboplastin time is rarely necessary unless a patient is receiving heparin, and the prothrombin time is of essentially no use to monitor heparin’s effects. Neither is informative during low molecular weight heparin treatment, whereas factor 10A is helpful.

3. Platelet numbers correlate roughly with the tendency to bleed. At platelet counts greater than 50,000/mm$^3$, the risk of spontaneous bleeding is low, platelet transfusions are rarely necessary, and most procedures can be safely performed, provided that platelets function normally. By contrast, platelet counts less than 20,000 mm$^3$ are associated with spontaneous hemorrhage and are often treated with platelet transfusions. Platelet counts do not provide information about platelet function.

4. Whereas most bleeding disorders seen in the ICU are the result of acquired deficiencies of multiple clotting factors, most hereditary disorders stem from a single soluble factor deficiency. Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX) deficiency constitute 90% or more of clinically significant hereditary bleeding disorders. Because these two conditions can be detected by an activated partial thromboplastin time and are rarely the result of a spontaneous mutation, they can be easily excluded from consideration by family history and a simple blood test.

5. Liver disease, vitamin K deficiency, dilutional coagulopathy, and disseminated intravascular coagulation are the most common soluble factor problems encountered in the ICU. All can produce elevations of the prothrombin time and activated partial thromboplastin time. The presence of high levels of FDPs and a lower platelet count favors disseminated intravascular coagulation. Vitamin K deficiency and liver disease can often be distinguished by searching for additional historical or chemical evidence of a liver disease, especially a problem of synthetic function. Although dilution and disseminated intravascular coagulation can appear similar, dilutional coagulopathy is less likely to exhibit fibrin degradation products.

6. When using unfractionated heparin for thromboembolism, a loading dose followed by a continuous infusion is almost always necessary to achieve the usual target level of anticoagulation of an activated partial thromboplastin time 1.5 to 2 times baseline. Subtherapeutic activated partial thromboplastin times usually require an additional bolus and increases in infusion rate of 20% to 25% for correction. Many centers now employ anti-factor Xa assays to manage heparin therapy. Quality and acceptance of the anti-factor Xa assay are increasing. For most patients, low molecular weight heparins are safer, more effective alternatives that do not require in vitro monitoring.

7. New direct oral anticoagulants offer improved protection against stroke related to atrial fibrillation and are safer than warfarin. Reversal of these agents in emergent situations will remain challenging until a full array of antidotes is developed.

8. Clues that could trigger a laboratory search for a thrombotic condition are unprovoked clotting, clotting at an early age, repeated episodes of thrombosis, a positive family history of clotting, and a history of repeated spontaneous abortions.
In the intensive care unit (ICU), bleeding disorders are diagnosed more commonly than clotting disorders, even though diseases related to localized thrombosis (e.g., stroke, myocardial infarction, thromboembolism) are substantially more common and lethal. The disparity in diagnostic rates occurs in part because bleeding is visible, whereas thrombotic conditions have more protean manifestations. This variation is also explained by the fact that the most commonly available in vitro laboratory tests reflect defective clotting, not a thrombotic tendency, and less is known about disorders producing excessive thrombosis. Although no single routine laboratory test is indicative of overall clotting function, nearly all clinically significant bleeding disorders can be screened for by adding an activated partial thromboplastin time (aPTT) and platelet count to the prothrombin time (PT) or INR. Fibrinogen level is frequently not assessed, even though in the patient with major bleeding, it is required to a greater extent than other hemostatic proteins. Unfortunately, no abnormal in vitro clotting test value accurately predicts that bleeding will occur, nor do normal values preclude bleeding.

BLEEDING DISORDERS

Vascular endothelium, clotting proteins, and platelets are the components of hemostasis. Only when two or more of these hemostatic pathways are defective are spontaneous or uncontrollable hemorrhage likely; impairment of any single factor seldom provokes clinical bleeding. However, because many patients are in the ICU because they have conditions that breach vascular integrity (e.g., surgery, trauma, and sepsis), it only requires the addition of a platelet or soluble factor disorder to induce bleeding.

Approach to the Bleeding Patient

History

The history provides important clues to the etiology of bleeding. With few exceptions, the rare hereditary disorders produce deficiency or dysfunction of a single clotting factor, whereas the much more common acquired disorders cause multiple factor abnormalities. All congenital bleeding disorders are inherited in an autosomal fashion, except for the sex-linked recessive hemophilies and the very rare Wiskott-Aldrich syndrome. The most common inherited bleeding disorder is von Willebrand disease (vWD), an autosomal dominant condition that produces combined platelet-vessel wall dysfunction in up to 1% of the population. Fortunately, despite its prevalence, vWD is usually so mild that it often remains undiagnosed. Although much less common, the hemophilias are the most likely genetic disorders to result in clinically significant bleeding. Deficiency of factor VIII (hemophilia A) may be up to ten times more common than the milder factor IX deficiency (hemophilia B). Unlike vWD, which affects men and women with equal frequency, the X-linked recessive inheritance pattern of the hemophilias dictates an almost exclusively male occurrence. (Some female carriers have factor levels as low as 50% and can exhibit mild bleeding tendencies.) All other inherited factor deficiencies are very rare autosomal recessive conditions; for these reasons, a thorough negative family history virtually excludes a diagnosis of hereditary coagulopathy. Furthermore, almost all inherited coagulation disorders manifest in childhood, making a new diagnosis in an adult a distinct rarity.

In taking the history, patient reports of “easy bleeding,” excessive bruising, or heavy menses are so common and nonspecific that they are all but useless. Detailed answers to the following questions should be sought: (1) Has there been excessive bleeding during or after surgery (especially oral surgery) or following significant trauma? (2) Has bleeding required transfusion or reoperation? The answers to these two questions can be very telling; an adult who has never experienced significant bleeding spontaneously or following surgery or trauma is extremely unlikely to have a hereditary disorder (at least one of clinical significance). If there is a suggestive history, the following questions help confirm the problem and point to the cause: (1) When did hemorrhage occur in relation to trauma or surgery? (Intraoperative bleeding suggests a platelet or vessel disorder, whereas delayed bleeding is more indicative of a soluble factor problem.) (2) What drugs have been taken? Particular attention should be paid to drugs affecting platelet numbers (e.g., immunosuppressive chemotherapy and alcohol) or function (e.g., aspirin, clopidogrel, glycoprotein IIb/IIIa inhibitors, and nonsteroidal anti-inflammatory agents) or those impairing synthesis of vitamin K-
dependent clotting proteins (e.g., warfarin and antibiotics).

**Physical Examination**

Petechiae (especially in dependent, high venous pressure areas), purpura, and persistent oozing from skin punctures or mucosal sites are most characteristic of platelet disorders. Palpable purpura is a sign of small artery occlusion usually associated with vasculitis of collagen-vascular disease (i.e., polyarteritis, systemic lupus erythematosus [SLE]), endocarditis, or severe sepsis. Larger vessel occlusions from disseminated intravascular coagulation (DIC) may cause the extensive ecchymoses of purpura fulminans. By contrast, factor deficiencies (especially the hemophilias) usually cause deep muscle and joint bleeding that results in ecchymoses, hematomas, and, the most characteristic feature, hemarthroses.

**Laboratory Tests**

Basic screening tests of clotting function are indicated for patients undergoing surgery or invasive procedures and for those with a history that suggests a bleeding disorder. Clotting tests are also useful in patients undergoing massive transfusion, anticoagulation, or thrombolytic therapy. When indicated, a platelet count, PT, and aPTT usually suffice to exclude clinically important bleeding disorders (Fig. 30-1). (Neither the PT nor aPTT will detect factor XIII deficiency, fortunately a rare cause of hemorrhage.) Not all prolongations of the PT and/or aPTT signify an increased risk of hemorrhage. For example, deficiencies of factor XII, high molecular weight kininogen (HMWK) or prekallikrein or the presence of anticardiolipin antibody, also known as lupus anticoagulant, may prolong in vitro clotting tests without increasing bleeding risk. (In fact, anticardiolipin antibodies are more likely to result in clotting than bleeding.)

It has long been routine to measure PT, aPTT, and platelet count at the time of admission in almost all hospitalized patients. However, in the absence of a history suggesting hemophilia, vWD, or heparin use, measurement of the aPTT is extremely unlikely to yield a true positive abnormality and thus is wasteful of money and blood. Likewise, the common practice of measuring both the PT and aPTT in all patients receiving warfarin or heparin is also uneconomical; aPTT determinations are unnecessary during therapy with only warfarin, and PT measurements rarely add to the care of patients receiving only heparin. PT and aPTT ordering should be unlinked and tailored to the specific clinical indications.
FIGURE 30-1. Coagulation cascade with factors evaluated in routine coagulation assays. Factors in the overlapping triangular area cause abnormality of aPTT and PT. aPTT, activated partial thromboplastin time; TT, thrombin time; PT, prothrombin time.

PLATELET DISORDERS

Thrombocytopenia
Thrombocytopenia, the most common coagulation disorder among ICU patients, is not only associated with an increased risk of bleeding but serves as an independent predictor of outcome. This problem is seen in 20% of medical patients and a third of surgical patients. Normally, platelet counts average 250,000/mm$^3$ and display little day-to-day variability in individuals; therefore, a 50% decline in platelet levels usually represents a significant change. In the absence of bleeding, most physicians do not display concern until levels dip to 100,000/mm$^3$ (<10 platelets per high-power field on peripheral blood smear). As platelet counts fall below this threshold, bleeding risk increases progressively and even more so if functional platelet abnormalities coexist. A search for the cause of thrombocytopenia and periodic rechecking of platelet counts is prudent when levels decrease by 50% and certainly when they reach 100,000/mm$^3$. Although counts greater than 50,000/mm$^3$ are acceptable for most types of surgery,
greater than 100,000/mm$^3$ are preferred for cardiac procedures or neurosurgery. Spontaneous bleeding is rare with counts greater than 20,000/mm$^3$ normally functioning platelets, but at this level, bleeding may occur even with minor trauma. When counts fall below 20,000/mm$^3$, spontaneous bleeding is possible. Normally, about 10% of platelets appear “large” on the peripheral smear, reflecting recent production. These young platelets produced by an active marrow are more hemostatically effective. Therefore, at any given count, bleeding is more likely to occur if thrombocytopenia results from impaired platelet production (rather than increased destruction). Common causes of thrombocytopenia are outlined in Table 30-1. Among all causes, idiopathic thrombocytopenia (ITP), acute leukemia, and aplastic crisis are the most likely causes of severe thrombocytopenia (<10,000/mm$^3$).

Mechanistically, thrombocytopenia is usually classified as a problem of production or destruction, but low counts can also result from dilution, splenic sequestration, or artifact. Spurious thrombocytopenia can occur when platelets form large clumps after being exposed to the anticoagulant EDTA. Spurious thrombocytopenia can be detected by automated testing of a heparinized sample or directly examining a bedside peripheral smear. Although there are no reliable rules of thumb, replacement of the entire blood volume within a day, or half within 3 to 4 hours, is typically required to precipitate a dilutional coagulopathy. The occurrence of dilutional coagulopathy is so variable that a strategy that advocates a fixed recipe of blood product replacement does not make sense. Although one might suspect that mild thrombocytopenia would result from dilution, surprisingly in cases where 20 or more units of blood products are transfused, platelet counts less than 50,000/mm$^3$ are common. Dilutional coagulopathy is also frequently compounded by hypothermia resulting from ambient exposure, infusion of large volumes of cool fluids, and acidosis resulting from underperfusion and infusion of acidic fluids.

Table 30-1. Causes of Thrombocytopenia

<table>
<thead>
<tr>
<th>Production Defects</th>
<th>Consumption Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPAIRED PRODUCTION</td>
<td>IMMUNE-MEDIATED DESTRUCTION</td>
</tr>
<tr>
<td>Drugs (alcohol, chemotherapy)</td>
<td>ITP</td>
</tr>
<tr>
<td>Infection (measles, mumps, EBV, TB, HIV, parvovirus, hepatitis C)</td>
<td>Drugs (heparin, quinine, valproic acid, sulfonamide, phenytoin)</td>
</tr>
<tr>
<td>Myelodysplasia</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Radiation</td>
<td>Systemic lupus</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Alloimmunization/posttransfusion</td>
</tr>
<tr>
<td></td>
<td>Antiphospholipid syndrome</td>
</tr>
<tr>
<td>INEFFECTIVE PRODUCTION</td>
<td>NON-IMMUNE-MEDIATED DESTRUCTION</td>
</tr>
<tr>
<td>B$_{12}$/folate deficiency</td>
<td>DIC</td>
</tr>
<tr>
<td>Myeloproliferative disease</td>
<td>Cardiopulmonary bypass</td>
</tr>
<tr>
<td></td>
<td>Splenomegaly</td>
</tr>
<tr>
<td></td>
<td>Prosthetic cardiac valves</td>
</tr>
<tr>
<td></td>
<td>Thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td></td>
<td>Hemolytic uremic syndrome</td>
</tr>
<tr>
<td></td>
<td>Preeclampsia and HELLP syndrome</td>
</tr>
<tr>
<td></td>
<td>Ventricular assist devices</td>
</tr>
</tbody>
</table>
Because up to one third of all platelets are in the spleen at any given time, splenic enlargement, typically from the portal hypertension of cirrhosis, and ITP can lower circulating counts. Anemia, leukopenia, and a normal or hyperplastic marrow usually accompany thrombocytopenia from hypersplenism.

**Impaired Production**

In the ICU, isolated platelet production defects are uncommon; when inadequate production accounts for thrombocytopenia, anemia and leukopenia usually coexist (i.e., complete marrow failure). In such cases, platelets are small and bone marrow examination shows a decreased number of megakaryocytes. Marrow failure may result from alcohol or radiation; a deficiency of vitamin B₁₂ or folate; infection with hepatitis B, Epstein-Barr virus, parvovirus, or cytomegalovirus; cytotoxic chemotherapy; or marrow infiltration with tumor, fibrosis, or granuloma. Selective failure of platelet production may occur with the use of gold, sulfas, and thiazides.

**Increased Consumption**

Excessive platelet consumption is the most common cause of thrombocytopenia and may be due to immunologic or nonimmunologic mechanisms. Laboratory clues to excessive platelet consumption include disproportionate numbers of large (young) platelets on peripheral smear and an increased number of marrow megakaryocytes. Nonimmunologic platelet consumption occurs in DIC, severe sepsis, some malignancies, microangiopathic hemolysis, and following cardiopulmonary bypass and splenic sequestration. Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are other nonimmunologic cause of thrombocytopenia in which platelets aggregate with abnormally large von Willebrand factor (vWF) multimers that result from a deficiency in a vWF-cleaving protease. The often profound thrombocytopenia is accompanied by elevated serum lactate dehydrogenase (LDH) levels and the presence of schistocytes on the peripheral smear representing mechanical erythrocyte destruction. Only microangiopathic hemolytic anemia and thrombocytopenia are required for the diagnosis, despite the description of a classic “pentad,” which also includes renal dysfunction, neurologic abnormalities, and low-grade fever. Numerous conditions, including cancer, pregnancy, antiphospholipid antibody (APLA) syndrome, and pneumococcal infection, can be associated with “TTP-like” syndromes as can medications, such as cyclosporine, clopidogrel, and some chemotherapeutic agents. The absence of significant fever and normal aPTT and PT seen with TTP-HUS can sometimes help differentiate it from DIC, which also can exhibit schistocytes on the peripheral smear. Unfortunately, increased coagulation parameters are not universally present in DIC, making the distinction difficult at times. HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) of pregnancy represents another condition with hemolysis and thrombocytopenia that may be difficult to discriminate from TTP-HUS. Elevated liver enzymes may be helpful in differentiating the two, but pregnancy itself is not distinguishing because it is also a risk factor for TTP. Because HELLP syndrome usually resolves within 72 hours of delivery, continued worsening of thrombocytopenia beyond this time should prompt strong consideration of TTP-HUS.

Immune-mediated thrombocytopenia occurs via production of platelet antibodies with subsequent destruction. The antibodies can be idiopathic, or induced by drugs, infections (e.g., cytomegalovirus, human immunodeficiency virus, Epstein-Barr virus, parvovirus), or alloimmune following transfusion or transplantation. Many drugs have been implicated as causes of thrombocytopenia. Drug-induced destruction of platelets usually occurs via the formation of
antiplatelet antibodies, which bind normal platelets in the presence of the sensitizing drug but a few drugs, such as procainamide, induce autoantibodies that react with platelets even in the absence of the drug. A third mechanism of drug-induced thrombocytopenia involves a direct interaction between drug and platelets resulting in immune destruction. Tirofiban, for example, interacts with the glycoprotein IIb/IIIa receptor on platelets, changing their shape and thereby facilitating antibody recognition. Heparin, one of the most common drugs associated with thrombocytopenia, similarly binds platelet factor 4 (PF4) forming an immune complex, which is recognized and destroyed.

Drug-induced thrombocytopenia can be overlooked because its onset is often a week or more after beginning the medication and there are no distinguishing clinical features. Nonetheless, recognition is important because the problem may sometimes be reversed by simply discontinuing the offending agent. After drug discontinuation, platelet counts often rise substantially within 5 days, but full recovery may take 3 to 4 weeks. Platelet transfusions and corticosteroids may help restore platelet counts rapidly once the inciting drug is removed.

In acute ITP, immunologic platelet destruction usually follows a childhood viral illness. Steroids are frequently helpful if thrombocytopenia persists more than several weeks. In adults, ITP usually presents as a chronic disease, with counts ranging from 20,000 to 80,000/mm$^3$. The spleen is the major site of platelet destruction of the IgG-coated platelets. Splenectomy is indicated in the 10% to 20% of patients who fail to respond to steroids or immune globulin. Anemia in ITP is secondary to blood loss, not immune hemolysis. Interestingly, despite sometimes profound reductions in platelet count, life-threatening bleeding is rare.

**Platelet Dysfunction**

By impairing platelet function, drug effects, uremia, DIC, leukemia, vWD, and paraproteinemia can cause bleeding despite normal platelet counts. If performed, the bleeding time is abnormal. The most common drugs to impair platelet function are listed in Table 30-2. Function may be impaired by drug combinations even when any single drug acting alone would be well tolerated. (The most common combinations causing platelet dysfunction are aspirin and alcohol and aspirin and clopidogrel.) Aspirin impairs platelet function irreversibly, so hemostasis is restored only by transfusion or formation of new platelets over a period of days. (Platelets can be generated at a rate sufficient to restore functioning levels by 10% to 30% each day.) The glycoprotein IIb/IIIa inhibitors alone or in combination with aspirin are commonly used to deter thrombosis after coronary interventions, and although all of these agents impair platelet function, the effects of abciximab persist until new platelets are produced. Similarly, clopidogrel impairs coagulation for days by inhibiting adenosine diphosphate-induced platelet aggregation preventing activation of the IIb/IIIa mechanism. In bleeding patients exposed to these medications, discontinuation of the drug may not be sufficient to return platelet function to normal and platelet transfusion may be needed. Alcohol inhibits platelet production and action in several ways. Heavy alcohol usage predisposes to trauma, encourages nutritional deficiencies, and directly injures the marrow. Given in high doses, most penicillins bind to the platelet surface, preventing interaction with vWF. (This does not occur with methicillin or cephalosporins.)

Although patients with end-stage renal disease may have mild thrombocytopenia, more often platelet numbers are normal, but their function is not. The pathophysiology of “uremic coagulopathy” is uncertain but likely multifactorial. One factor is anemia causing platelets to travel in a more midstream position within vessels, rendering them further away and less likely to react to endothelial damage. In addition, uremic toxins result in dysfunctional vWF and vWF-factor VIII complex and impaired platelet aggregation.

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**Table 30-2. Drugs Inhibiting Platelet Function**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td></td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs (NSAIDs)</td>
<td></td>
</tr>
</tbody>
</table>
Therapy of Platelet Dysfunction

Bleeding rarely occurs in patients with platelet dysfunction alone. As a first step, potentially offending medications should be discontinued. Unless sequestered or destroyed, transfused platelets quickly restore coagulation competency. Platelet transfusions will effectively correct dysfunction induced by aspirin, clopidogrel, or the cardiac bypass pump. Platelet transfusion is also transiently useful when the platelet environment is abnormal, as in uremia, paraproteinemia, or after treatment with high-dose penicillin or dextran. However, it is better to correct the underlying defect using dialysis, plasmapheresis, or by discontinuing the offending drug.

Treatment of chronic dialysis in patients who are bleeding requires a multifaceted approach, including adequate dialysis to address uremia. Functional defects caused by uremia and vWD may at least temporarily be corrected with fresh frozen plasma (FFP), arginine vasopressin (also known as desmopressin [DDAVP]), or cryoprecipitate. By releasing factor VIII/vWF multimers, DDAVP in doses of 0.3 μg/kg IV or 3 μg/kg intranasally corrects clotting abnormalities in at least half of all patients within 1 hour. Unfortunately, effectiveness is limited by tachyphylaxis, which occurs usually by the second dose. By increasing the levels of functional factor VIII, vWF, and fibrinogen, cryoprecipitate is a useful strategy particularly in uremic coagulopathy. For long-term therapy, estrogens may be helpful. Although mechanism of action is not entirely understood, estradiol working through estrogen receptors can increase clotting within a day of starting therapy.

INTERPRETATION OF ABNORMAL CLOTTING TESTS

Surprisingly, a common cause of an abnormal clotting assay is not a physiological problem or even laboratory error but rather an improperly obtained sample. There are several common causes of this so-called preanalytical error. Accurate results from aPTT and PT testing require a specific ratio (9:1) of plasma to anticoagulant (typically sodium citrate in a “blue top” tube). If the tube is underfilled, both values will be prolonged. Conversely, if the tube is forcefully overfilled, clotting times will be shortened. Another potential source of error occurs if blood is contaminated with a second anticoagulant. This error typically occurs in one of two ways: blood is drawn from a heparin-containing catheter; or blood is placed into the wrong tube and then transferred to the correct tube. For example, blood initially drawn into an EDTA or heparin-containing tube, which is then transferred to a citrate tube, will yield prolonged PT and aPTT values. Another problem results when blood is not promptly and gently mixed with anticoagulant. For example, initial collection of blood into a tube not containing anticoagulant, delay in transferring blood from a syringe to an anticoagulant-containing tube, and failure to mix blood in with the anticoagulant all can artificially prolong the PT and aPTT. Conversely, hemolysis or excessively vigorous agitation of blood with citrate will artificially shorten the PT and aPTT. Excessive tourniquet time elevates vWF and factor VIII levels also resulting in falsely shortened PT and aPTT. Because both the aPTT and PT are performed on platelet-depleted plasma, thrombocytopenia does not alter their in vitro values.

In general, an isolated PT prolongation of 2 or 3 seconds or an aPTT prolonged by as much as 5 seconds should not raise concern in the absence of bleeding. In fact, aPTT abnormalities of such a magnitude usually do not warrant further investigation because very few disorders occurring in the ICU cause an isolated progressive prolongation of the aPTT (exception: unfractionated heparin [UFH] therapy), and the history will dictate further evaluation for hemophilia or vWD. On the other hand, it is often prudent to recheck a prolonged PT of even a few seconds because many diseases or interventions occurring in the ICU can progressively extend the PT (e.g., antibiotic
therapy, starvation, progressive hepatic failure).

The PT or aPTT may be prolonged individually or together. Each potential combination of abnormalities suggests a limited specific set of diagnostic possibilities and an optimal plan for evaluation. Potential diagnoses and their evaluation are summarized in Table 30-3 and discussed below.

**Prothrombin Time**

The PT is a test of the tissue factor (formerly extrinsic) clotting pathway in which factor VII is activated by adding complete tissue thromboplastin and calcium to a platelet-depleted citrated sample. This process sequentially triggers factors X, V, and II and then fibrinogen. Because the endpoint of the test is clot formation, deficiencies of factor VII (or any factor at or distal to factor X) can prolong the PT (Fig. 30-1). The PT is relatively resistant to change, typically requiring factor levels to fall to 10% of normal or less before becoming prolonged. An acquired inhibitor to one of these same factors will also prolong the PT. (Inhibitors can be detected by mixing the suspect plasma in a 1:1 ratio with normal plasma; a persistently abnormal PT indicates presence of an inhibitor.) Common causes of a prolonged PT are listed in Table 30-3. Even though heparin inhibits some factors in this test of the tissue factor pathway, it is a rare cause of significant PT prolongation because there are fewer factors sensitive to heparin in the tissue factor pathway and a greater degree of inhibition is required for PT prolongation. In addition, some PT assay systems contain heparin-neutralizing compounds. (Massive heparin levels can overcome these inhibitors.)

<table>
<thead>
<tr>
<th>Prolonged Prothrombin Time</th>
<th>Prolonged Partial Thromboplastin Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spurious results (underfilled tube)</td>
<td>Spurious results (underfilled tube)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Vitamin K deficiency/malnutrition</td>
<td>Polycythemia</td>
</tr>
<tr>
<td>Warfarin therapy</td>
<td>Delay in performing assay</td>
</tr>
<tr>
<td>Broad-spectrum antibiotic therapy</td>
<td>Heparin</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>Antiphospholipid antibodies</td>
</tr>
<tr>
<td>Dilutional coagulopathy</td>
<td>Hemophilias A and B</td>
</tr>
<tr>
<td>Circulating anticoagulants (i.e., antiphospholipid antibodies)</td>
<td>von Willebrand disease</td>
</tr>
<tr>
<td>Salicylate poisoning</td>
<td></td>
</tr>
<tr>
<td>Massive heparin overdose</td>
<td></td>
</tr>
</tbody>
</table>

The very uncommon combination of a normal aPTT with a prolonged PT is uniquely explained by a deficiency of factor VII. This combination is rarely seen on a chronic basis (i.e., genetic deficiency of factor VII or acquired
inhibitor), but because factor VII has the shortest half-life of all vitamin K-dependent clotting proteins (approx. 6 hours), transient, isolated prolongation of PT can occur in early vitamin K deficiency, hepatic failure, DIC, or warfarin therapy.

**Activated Partial Thromboplastin Time**

The aPTT tests the contact activation (formerly intrinsic) pathway by adding kaolin, silica or other particulate, and phospholipid (in lieu of complete thromboplastin) to activate coagulation, hence the name *activated partial* thromboplastin time. In sequence, factor XII activates factor XI, then IX, and VIII, which then triggers the common sequence of factor X to V through fibrin formation. Hence, the aPTT tests all factors except for VII and XIII, making it a sensitive overall test of clotting abnormalities but less specific than the PT for the same reason (see Fig. 30-1). Single factors unique to the contact activation pathway must decline to only 15% to 30% of normal before the aPTT is prolonged. Milder deficiencies of multiple factors can also prolong the aPTT. In the absence of heparin, the discovery of a normal PT with a prolonged aPTT usually indicates an inherited deficiency or dysfunction of factors VIII, IX, XI, or XII (most often hemophilia A or B or vWD). Common causes of a prolonged aPTT are listed in Table 30-3. Inherited disorders of the common pathway (factors II, V, X, and fibrinogen) are rarely to blame. Among these, fibrinogen deficiency can be quickly excluded by direct measurement. Prekallikrein, HMWK, and factor XII deficiencies will also prolong the aPTT, but the former two are rare, and none of the three increases the risk of bleeding despite altering the aPTT.

### Table 30-4. Interpretation of PT and aPTT Tests

<table>
<thead>
<tr>
<th>Activated aPTT</th>
<th>Prothrombin Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Defect: Factor XIII&lt;br&gt;Frequency: Very rare&lt;br&gt;Dx test: Quantitative factor XIII assay has largely replaced the urea solubility assay</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Defect: Contact pathway (e.g., heparin, Hemophilias A and B, von Willebrand's), antiphospholipid antibody, coagulation protein antibody, unfractionated heparin, deficiency factor VIII, IX, XI, XII&lt;br&gt;Frequency: Uncommon&lt;br&gt;Dx test (exclude heparin) then: If bleeding, check VIII, IX, XI levels; no bleeding, check prekallikrein, XII, high molecular weight kininogen</td>
</tr>
</tbody>
</table>

### Combined PT and aPTT Abnormalities

Because the contact and tissue factor pathways share multiple factors (X through II), diseases or therapies altering one pathway often affect the other. When both the PT and aPTT are abnormal, simultaneous treatment with heparin and warfarin or an acquired bleeding disorder affecting multiple factors (e.g., liver disease, DIC, fibrinolytic therapy)
is almost always responsible. Table 30-4 provides an overview of the diseases and defects in which isolated or combined abnormalities of the PT and aPTT are seen.

**Anti-Xa Activity Assay**

One test being used with increasing frequency because of the popularity of low molecular weight heparins (LMWHs) is the anti-Xa activity assay. Methodology is straightforward: an excess of factor Xa and antithrombin (AT) are added to platelet-poor, citrated patient plasma. Any heparinoid in the test sample binds to the exogenous AT impairing the activity of the added Xa, which is detected as a decrease in the cleavage of an added chromogenic substrate, relative to control. LMWHs and direct Xa inhibitors such as fondaparinux bind to AT through a 5-oligosaccharide sequence, but unlike the longer UFH, do not have sufficient length to bind to thrombin (factor IIa). As a result, the PT and aPTT demonstrate minimal changes (on average 1 to 4 seconds) despite effective anticoagulation.

**Activated Clotting Time**

In locations like the cardiac catheterization lab, where a real-time estimate of clotting is necessary, the activated clotting time (ACT) is often used, especially to monitor UFH or bivalirudin activity. The ACT is a nonspecific test, which reports the time for an activating agent (e.g., celite, kaolin, glass particles) to produce clot in whole blood, thereby evaluating soluble factor and platelet function. Because neither the reagents nor clot detection method (e.g., resistance to mechanical deformation of clot or changes in the electrical or mechanical properties of the blood) is standardized, results of different assay systems are not equivalent and the ACT correlates poorly with aPTT, PT, and anti-Xa assays.

**Thrombin Time**

The thrombin time is a test of the final step in the coagulation cascade, performed by adding thrombin to an anticoagulated sample, thereby converting fibrinogen to fibrin (see Fig. 30-1). Because only the terminal step in a complex clotting array is evaluated by this test, it detects a limited number of clotting abnormalities. Fibrinogen levels less than 100 mg/dL, most commonly from DIC, thrombolytic therapy, or dysfunctional fibrinogen, may prolong the thrombin time. UFH, fibrin degradation products (FDPs), and abnormal immunoglobulins also prolong the thrombin time by interfering with thrombin-induced fibrinogen conversion. (If heparin is the etiology, the reptilase time will be normal.) Direct thrombin inhibitors (e.g., hirudin, argatroban) will not only prolong the PT, aPTT, and thrombin time but the reptilase time as well.

**Bleeding Time and Platelet Function**

Together, a platelet count and bleeding time effectively screen for platelet problems by testing the platelet number, adhesion, and aggregation. The bleeding time is primarily a test of platelet function but is also influenced by platelet number and tissue fragility and edema. Accuracy is highly subject to technician expertise. As a general rule, the bleeding time becomes a less reliable index of platelet function when counts fall below 100,000/mm$^3$, will often be prolonged if platelets number is less than 80,000/mm$^3$, and will almost always be prolonged if counts dip below 50,000/mm$^3$. Unfortunately, a normal or high platelet count does not ensure a normal bleeding time, as function may be selectively impaired. The bleeding time is often abnormal in patients with uremia and in those receiving drugs that impair platelet function (e.g., aspirin and other nonsteroidal anti-inflammatory drugs, β-lactam antibiotics, and direct thrombin or IIb/IIIa inhibitors). Bleeding time is also prolonged by rare, inherited platelet disorders (Bernard-Soulier, Glanzmann syndrome, and Wiskott-Aldrich syndrome), by vWD, and by severe hypofibrinogenemia. One common and important artifact that can prolong bleeding time is anemia. By altering blood rheology and diluting platelets in a larger volume of plasma, anemia prolongs bleeding time. The degree of bleeding time prolongation correlates poorly with the tendency to bleed. Because of both the technical difficulty and limited predictive value of bleeding times, they are rarely performed in critically ill patients. Many centers use the automated PFA 100 assay, which significantly
improves precision and reproducibility from the bleeding time.

**Inhibitor Testing**

Roughly, only 30% activity of each clotting factor is needed to result in normal clotting assays; hence, combining equal portions of normal plasma (or a standardized reagent) and plasma from a patient with a factor deficiency will yield normal PT and aPTT results, unless a factor inhibitor (e.g., anticardiolipin antibody, factor VIII inhibitor) is present.

**Fibrinogen Levels and Fibrin Degradation Products**

Fibrinogen levels may be reduced as a result of impaired production or increased consumption. Because fibrinogen is an acute-phase reactant released from the liver, it may be elevated in hepatitis or other conditions that cause liver inflammation (e.g., severe sepsis). Therefore, even if consumption is increased, fibrinogen levels may remain in the normal range.

The term FDP is general one that describes the breakdown products of fibrin and fibrinogen generated by the enzymatic action of plasmin. The D-dimer is a specific subtype of FDP produced only by degradation of fibrin from an intact clot. Unfortunately, both assays lack specificity and are positive in patients with thrombotic diseases (e.g., venous thromboembolism, myocardial infarction, and in DIC). In fact, both can be elevated in patients with cancer and pregnancy, and because of impaired hepatic clearance, chronic liver disease can also result in elevated levels.

Commercially available assay methods differ significantly (i.e., latex or red blood cell agglutination or ELISA) resulting in widely divergent sensitivities. If using a D-dimer assay as an adjunctive test for thromboembolic disease diagnosis, it is imperative to use an ultrasensitive assay to avoid false-negative results. In general, assays using latex agglutination methods are least sensitive. Even in the very unlikely event, an inpatient's D-dimer assay is negative; it is imprudent to use this test alone as definitive evidence of absence of clot (also, see Chapter 23). By contrast, a negative sensitive D-dimer assay performed in an outpatient at low risk for thromboembolism all but excludes the disease.

**SPECIFIC CLOTTING DISORDERS**

**Heparin-Induced Thrombocytopenia**

Two forms of heparin-induced thrombocytopenia (HIT) are described. Type I is a common, mild, transient, self-limited, nonimmunologic variety that appears quickly (<5 days) after initiating heparin. Type I HIT occurs in up to 20% of heparin-exposed patients but is not associated with bleeding or clotting complications and does not necessitate discontinuing heparin therapy. The second more serious type of HIT (type II) is the result of IgG antibodies that cross-react with heparin and PF4 antigens. Onset is usually about 1 week after initiation of heparin but may occur as rapidly as 24 hours in a presensitized patient. Clinical clues to HIT are summarized in Table 30-5. Although both forms of HIT are more common among patients receiving high-dose UFH, even the modest amounts used for subcutaneous deep venous thrombosis (DVT) prophylaxis or intravenous catheter flushing can cause disease. An estimated 1% to 5% of UFH recipients will develop type II HIT, but the syndrome is significantly (perhaps 10-fold) less common among patients receiving LMWHs. With type II HIT typically, platelets decline to the 50,000/mm\(^3\) range, but 10% to 15% of victims will maintain counts near 150,000/mm\(^3\). The diagnosis of HIT is confirmed by finding heparin cross-reacting antibodies that activate platelets resulting in serotonin release. (Unfortunately, the serotonin release assay is not widely available and rarely in a timely fashion; hence, many diagnoses are false positive made on the basis of tests for cross-reacting IgG antibodies alone.) Type II HIT is a serious problem with 50% of patients or more developing venous or arterial thrombosis. Ironically, despite thrombocytopenia, clotting (e.g., DVT, PE, stroke, myocardial infarction, limb arterial occlusion) is much more common than hemorrhage. Withdrawal of heparin is mandatory but not sufficient treatment, and thromboses have been reported up to a month after stopping heparin. In addition to the immediate discontinuation of heparin,
anticoagulation with a direct thrombin inhibitor (e.g., bivalirudin or argatroban) is usually indicated. Warfarin should be withheld until platelet counts rise above 100,000/mm$^3$ to avoid potentially worsening the situation by lowering protein C levels at a time the patient is prone to thrombosis. Platelet transfusions should be avoided if possible. Re-exposure of patients with confirmed type II HIT to heparin is controversial but is sometimes inescapable.

### Table 30-5. Clinical Situations to Suspect Heparin-Induced Thrombocytopenia

**Current Use of Heparin or Heparin Exposure within 40 Days and at Least One of the Following:**

- Platelets < 100,000/μL
- Platelets <50% of baseline or <50% of the maximum level if reactive thrombocytosis is present
- Platelets < baseline 5 d after open heart surgery
- New arterial or venous thrombotic event
- Inflammation or necrosis at heparin injection sites
- Acute allergic or anaphylactic reaction to a heparin bolus

**Recent Admission to a Hospital, Nursing, or Rehabilitation Facility Plus:**

- A new venous thromboembolic event
- A new arterial ischemic event

### Hemophilia

The hemophilias are sex-linked recessive diseases producing clinical bleeding in affected males. Spontaneous hemorrhage in hemophilia A (factor VIII deficiency) or hemophilia B (factor IX deficiency) usually occurs only when factor levels dip below 5% of normal (most commonly <1%). Therefore, heterozygous female carriers possessing 50% of normal factor VIII or IX levels are spared bleeding complications. Despite these guidelines, a less-than-ideal correlation exists between factor levels and bleeding tendency. Laboratory examination in both diseases most commonly reveals a prolonged aPTT, with normal PT, platelet count, bleeding time, and thrombin time. Specific levels of factors VIII and IX are required to distinguish hemophilia A from B.

The urgency of therapy must be guided by the amount and location of bleeding; massive hemorrhage or bleeding into the brain or upper airway is most urgent. Surgery and invasive procedures in hemophiliacs require maintenance of factor levels greater than 50% for 14 days following the procedure. In critical operative sites (e.g., brain, spinal cord), activities approaching 100% are desirable. Topical aminocaproic acid may be effective at controlling localized mucosal or venipuncture bleeding. Although factor VIII is present in FFP cryoprecipitate and factor VIII concentrates, recombinant factor VIII is the most practical replacement product because of safety and fluid volume considerations. The 8- to 12-hour half-life of transfused factor VIII typically mandates twice-daily dosing. Replacement of factor IX can be accomplished using FFP, purified factor IX concentrates (also known as prothrombin complex concentrates [PCCs]), or recombinant factor IX. PCCs contain factors VII, IX, and X as well as trace amounts of factors VIII, VIIa, and Xa, the concentrations of each varying by manufacturer. Care must be exercised in administration of PCCs, which may excessively activate clotting. The biological half-life of factor IX is longer than factor VIII, permitting once-daily dosing for most patients. Input of a hematologist may be helpful for navigating the complexities of this disease.

(For detailed recommendations on the replacement of factors VIII and IX, see Chapter 14.)
Liver Disease

Apart from its role in clearing FDPs, the liver produces albumin and all clotting factors except the factor VIII–vWF complex. Therefore, a low serum albumin concentration supports hepatic insufficiency as the etiology of the coagulation disorder. When the liver is responsible for a coagulopathy, laboratory examination typically reveals decreased fibrinogen, increased circulating levels of FDPs, prolonged PT and aPTT, and an increased thrombin time (because of FDPs). Such a laboratory pattern is identical to that seen with DIC; however, detecting D-dimers and fibrin monomers favors a diagnosis of DIC.

Liver disease and vitamin K deficiency decrease levels of factor VII, the vitamin K-dependent factor with the shortest half-life (6 hours). This reduction leads to early increases in the PT. Because multiple factors (II, VII, IX, and X) are deficient in liver disease, FFP is the replacement product of choice if immediate correction is necessary. In less urgent situations, vitamin K will usually suffice if there is a vestige of hepatic synthetic function. Vitamin K should also be given empirically to virtually all patients with liver-related coagulopathy because it is difficult to distinguish liver disease from pure vitamin K deficiency. In urgent situations, vitamin K can be given intravenously; in less urgent situations, oral dosing is sufficient. Platelet counts are usually normal in liver disease unless there is coexisting hypersplenism or DIC. When platelet counts are significantly decreased (<50,000/mm³), platelet concentrates may be administered but unfortunately are often ineffective.

In parallel with the reduction in coagulation factors seen with liver disease, there is similar reduction in the production of physiologic anticoagulants. Thus, patients with chronic liver disease and a prolonged PT are no longer considered to have a deficiency of coagulation factors because their coagulation is rebalanced and thrombin generation is usually normal. In such cases, there is no need to treat prolonged coagulation times in the absence of bleeding. If bleeding does occur in liver disease, then consensus guidelines recommend blood component management as determined by the results of the platelet count, PT, activated partial thromboplastin time, thrombin time, and fibrinogen. In patients with liver disease and laboratory tests indicating abnormal synthesis of coagulation factors, vitamin K should be routinely administered to aid in synthesis of coagulation factors.

Vitamin K Deficiency: Warfarin Excess

Vitamin K deficiency may develop in any patient deprived of a balanced diet for 7 to 14 days. Because antibiotics may eliminate the enteric bacteria required for the production of vitamin K when intake is insufficient, malnourished patients and those receiving broad-spectrum antibiotic therapy are at particular risk. Fat-soluble vitamin K is incompatible with many total parenteral nutrition preparations and, if omitted, must be given separately. Warfarin compounds induce vitamin K deficiency by preventing carboxylation to the active form. Malabsorption (from pancreatic insufficiency) and bile salt deficiency (from ductal obstruction) may also prevent vitamin K absorption.

Vitamin K is required for the formation of factors II, VII, IX, and X. Although depletion of vitamin K eventually extends both the PT and aPTT, prolongation of the PT is more marked and occurs earlier because factor VII (tissue factor pathway) has the shortest half-life of all clotting proteins. (Very rarely, vitamin K deficiency leads to seemingly paradoxical thrombosis by reducing the production of the anticlotting proteins C, S, and AT.) FFP corrects the clotting disorder of vitamin K deficiency very rapidly (two to four units usually suffice). Vitamin K alone usually corrects the deficiency within 24 hours if liver function is normal. However, when hepatic disease is far advanced, vitamin K is ineffective and is analogous to bringing raw materials to a factory that is closed.

When vitamin K is used to reverse warfarin effect, its dose and route of administration should be guided by the urgency of the situation and the anticipated need for resuming warfarin anticoagulation. For example, during life-threatening hemorrhage, FFP and a large dose of vitamin K (10 mg) can be given intravenously to a patient who will not have warfarin restarted. PCCs may also be employed. By contrast, for a patient with only an excessively prolonged PT who must continue on long-term anticoagulation (e.g., mechanical mitral valve), a small dose (1 to 2
mg) of vitamin K orally is the most appropriate course of therapy. Using large doses of vitamin K may prevent re-establishing warfarin anticoagulation for several days or more. In many centers, protocols are in place to rapidly reverse prolonged international normalized ratio (INR) values in patients with life-threatening bleeding (brain injury) or where emergency surgery is required.

**Renal Disease**

Bleeding in the setting of uremia often presents with ecchymosis, purpura, epistaxis, and bleeding from puncture sites because of impaired platelet function. Platelet dysfunction in renal disease is a result of complex changes including dysfunctional vWF, decreased production of thromboxane, increased levels of cyclic AMP and cyclic GMP, toxins, anemia, and altered platelet granules, all of which are necessary for adequate formation of a platelet plug. Anemia commonly accompanies renal disease, disrupting laminar flow and prolonging the bleeding time. Treatment of anemia partially corrects this problem. Renal disease also tends to impair fibrinolysis.

Dialysis, particularly peritoneal dialysis, improves platelet function. Erythropoietin, cryoprecipitate, conjugated estrogens, desmopressin, and tranexamic acid have all independently been shown to reduce bleeding time. In the past decade, citrate has also become popular as replacement anticoagulation in continuous renal replacement therapy, with a consequent reduction in bleeding tendency.

**Disseminated Intravascular Coagulation**

DIC should be strongly considered in any patient with the combination of diffuse bleeding or clotting, elevations in PT and aPTT, and a decreased platelet count. DIC is not self-perpetuating but requires continuous activation of the clotting mechanism. Such stimulation most frequently results from vascular damage or sepsis. In DIC, thrombin activation stimulates plasmin-mediated thrombolysis. FDPs are formed in this process. With concurrent clotting and fibrinolysis, factors V and VII, fibrinogen, and platelets are rapidly consumed. Bleeding results if consumption outstrips production. The causes of DIC are numerous but usually relate to tissue inflammation from infection, trauma, tumor, or release of the products of conception into the circulation. Cytotoxic drugs, heat stroke, envenomations, and shock, as well as vascular disruption (e.g., aortic aneurysm), may also cause DIC.

Diagnosis of DIC is usually straightforward. This lesion typically presents as hemorrhage; only 5% to 10% of cases present with microthrombi as the most prominent disorder. Early in the course, the aPTT may shorten as thromboplastin is released into the circulation. Later, the PT and aPTT are prolonged because of depletion of fibrinogen, factors V and VII, and the anticoagulant action of FDPs. The platelet count is usually less than 150,000/mm$^3$ and fibrinogen usually less than 150 mg%. (Fibrinogen concentration may be in the normal range if levels were initially elevated, as with hepatitis or pregnancy.) The hallmark of DIC is an increase in the levels of FDPs and D-dimer levels. Large platelets are usually seen on peripheral smear along with the fragmented red blood cells (RBCs) that suggest microangiopathic hemolysis. A laboratory picture similar to DIC may be seen in dilutional coagulopathy or in hepatic failure complicated by thrombocytopenia from splenic sequestration or platelet destruction.

The treatment of DIC associated with bleeding is to reverse the underlying cause and to replete consumed clotting factors. Sepsis is the most common cause of DIC. Thus, typically, treatment involves removal of dead or infected tissue and giving antibiotics if infection is strongly suspected. Platelets should be administered for severe thrombocytopenia. FFP may be used to replenish most soluble factors. Cryoprecipitate may be used to replace fibrinogen if levels are markedly depressed. The cornerstone for managing DIC remains elimination of the underlying cause. Further management may not be necessary in patients with mild abnormalities in coagulation and no evidence of overt bleeding. Guidelines recommend replacement of coagulation proteins and platelets in patients who are bleeding. Platelet transfusion is indicated to maintain a platelet level of more than 50,000/mm$^3$ along with administration of FFP to maintain prothrombin and aPTT less than 1.5 times normal control and INR ≤2.0. A source of fibrinogen is administered when needed to maintain a fibrinogen level >1.5 g/L.
Antifibrinolytic agents are contraindicated in the management of DIC, as the fibrinolytic system is required during recovery to insure dissolution of widespread fibrin. Some guidelines recommend administration of therapeutic doses of UFH in patients with a thrombotic phenotype (gangrene), but this recommendation is controversial because of difficulties in monitoring treatment in the patient who already has a prolonged aPTT. Finally, heparin given in this setting may provoke hemorrhage.

Dilutional Coagulopathy
Dilutional coagulopathy usually occurs with massive hemorrhage, when replacement of a substantial fraction of the circulating blood volume leads to washout of platelets and clotting factors. At onset of recognized bleeding and after 6 units of packed RBCs, it is prudent to begin regular monitoring of INR, platelet count, fibrinogen, and aPTT. Dilutional effects may not be seen before 10 or more units of PRBCs are transfused. If platelet counts fall below 50,000/mm$^3$, random donor platelets are recommended. INR increases can be corrected with FFP. In addition to replacing deficient clotting proteins, preventing hypothermia is essential to optimize clotting enzyme function. The major diagnostic dilemma is to separate dilutional coagulopathy (increased PT and aPTT with decreased platelet count) from DIC, a distinction that is aided by the FDP assay and D-dimer level. While awaiting laboratory confirmation, a reasonable strategy is to administer 2 to 4 units of FFP; if the clotting factor is dilutional, FFP will frequently correct the defect.

Acquired Inhibitors of Coagulation
Circulating anticoagulants are immunoglobulins that inhibit the action of clotting proteins. These inhibitors are most commonly present in patients with pregnancy, hemophilia, rheumatoid arthritis, cancer, systemic lupus, advanced age, and in association with certain drugs (e.g., penicillin and chlorpromazine). The most notable inhibitor interferes with the actions of factors II, V, IX, and X. Although termed the lupus anticoagulant, also known as antiphospholipid and anticardiolipin antibody, such proteins much more commonly promote thrombosis rather than hemorrhage. Screening for a circulating anticoagulant is done by performing a PT and aPTT on a mixture of equal parts of normal and patient plasma. If a simple factor deficiency is the cause of abnormal clotting, the addition of normal plasma will provide 50% activity and will normalize clotting tests. However, if an inhibitor is present, clotting tests remain abnormal. Circulating anticoagulants may increase only the more sensitive aPTT, mimicking the laboratory findings of hemophilia. Antiphospholipid antibodies are also commonly associated with mild thrombocytopenia. In urgent circumstances, therapy may include massive replacement of the affected factors or the use of activated factor X. In the long term, immunosuppressive therapy with cyclophosphamide, prednisone, or intravenous immune globulin may be helpful.

von Willebrand Disease
vWD, an autosomal dominant trait, decreases the activity of the factor VIII-vWF complex, thereby reducing the adherence of platelets to sites of vascular injury. vWD is usually subclinical but when overt, presents with hemorrhage after trauma, mucosal bleeding, or menorrhagia. Laboratory findings include an increased bleeding time with a normal platelet count and a prolonged aPTT. Because factor VIII-vWF is an acute-phase reactant, the physiological stress of illness or even hemorrhage may increase plasma factor levels, thereby obscuring the diagnosis.

vWD may be inherited or acquired. A personal and family history of easy bruising and bleeding should be sought. Acquired vWD can arise in association with autoantibodies as well as in myeloproliferative and lymphoproliferative disorders. Breakdown of high molecular weight vWF multimers because of intravascular or extracorporeal circuit shear stresses may also occur in patients receiving such interventions. Sufficiently high vascular shearing stresses may develop in extracorporeal circuits of membrane oxygenators and left ventricular assist devices.

The diagnosis of vWD is ultimately established by specialized testing including direct measurement of vWF, factor
VIII activity, ristocetin cofactor activity, and vWF collagen binding. Initial treatment for patients with clinically significant bleeding and vWD includes DDAVP, which releases vWF from vascular endothelial cells. For refractory bleeding and for patients with severe vWF deficiency, factor VIII concentrates, which also contain vWF or recombinant human vWF, should be administered. Other options for refractory bleeding include antifibrinolytic agents, epsilon aminocaproic acid, and tranexamic acid as well as human recombinant factor VIIa.

**Paraproteinemia**

When present in large amounts, serum proteins of the IgG, IgM, and IgA classes may impair clotting. Such problems usually occur in patients with myeloma or Waldenström macroglobulinemia. Plasmapheresis reduces the serum protein level and reverses the coagulopathy.

**Thrombolytic Therapy**

Almost any in vitro clotting test will confirm the presence of a “lytic state” during the administration of thrombolytic agents (e.g., tissue plasminogen activator [tPA], which is now used almost exclusively because of product availability and safety). The thrombin time, however, most directly monitors the effect of thrombolytic drugs by examining the final step in the clotting cascade (the conversion of fibrinogen to fibrin). As an index of the effectiveness of thrombolytic activity, the thrombin time should be maintained two to five times the baseline value when assessed 4 hours after the initiation of therapy. If bleeding occurs during thrombolytic therapy, cryoprecipitate and FFP can rapidly correct the clotting abnormalities. Because hemorrhage during thrombolytic therapy is usually a consequence of poor patient selection (e.g., elderly, traumatized) or the result of invasive procedures during the lytic period, most bleeding episodes can be avoided.

**Anticoagulant Therapy**

**Heparins**

Anticoagulation therapy often proves challenging because there are opposing risks of thrombosis from underdosing and risks of bleeding from excessive dosing. Unfortunately, current monitoring tests are only crude and indirect measures of the risk of clotting or bleeding. Serious bleeding during anticoagulation, however, usually indicates a coexisting disturbance of vascular integrity or platelet function. As a corollary, gastrointestinal or genitourinary tract hemorrhage occurring at therapeutic levels of anticoagulation usually indicates an underlying structural lesion. Recognized risk factors for anticoagulant-induced bleeding include advanced age, alcohol and antiplatelet agent use, and female gender. Characteristics of the heparins and fondaparinux are reviewed in Table 30-6.

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Table 30-6. Comparison of Pharmacokinetic Parameters, Dosing Frequencies, and Indications for UFH, LMWHs, Fondaparinux, and Argatroban

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>UFH</th>
<th>LMWH</th>
<th>Fondaparinux</th>
<th>Argatroban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enoxaparin</strong></td>
<td>Enhances AT effects on Factor Xa and thrombin. Binds non-specifically to plasma proteins.</td>
<td>Enhances AT effects more selectively on Factor Xa than on thrombin. Less binding to plasma proteins → more predictable dose response, less inter-patient variability.</td>
<td>Enhances anti-Xa activity of AT. Specificity for AT → no binding to other plasma proteins, good</td>
<td>Direct thrombin inhibitor.</td>
</tr>
<tr>
<td><strong>Dalteparin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Half-Life</strong></td>
<td>1-2 h</td>
<td>4.5-7 h</td>
<td>2-5 h</td>
<td>17-21 h</td>
</tr>
<tr>
<td>----------------</td>
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</tr>
<tr>
<td><strong>Reversal Agents</strong></td>
<td>Protamine Sulfate 1 mg neutralizes 100 units Calculated based on heparin given during the last 3-4 h</td>
<td>Protamine Sulfate (neutralizes 60% of activity) Based on time since LMWH was dosed: &lt;8 h—1 mg protamine per 1 mg LMWH 8-12 h—0.5 mg protamine per 1 mg LMWH &gt;12 h—Protamine not recommended</td>
<td>Not reversible by protamine Factor VII-limited data</td>
<td>Fresh Frozen Plasma Prothrombin Complex Concentrates for acute bleeding. No specific antidote.</td>
</tr>
<tr>
<td><strong>Routine Monitoring</strong></td>
<td>aPTT for IV drips</td>
<td>None</td>
<td>None</td>
<td>Routine monitoring aPTT, ACT for drips</td>
</tr>
<tr>
<td><strong>Dosing Frequency</strong></td>
<td>Treatment-Continuous drip</td>
<td>BID or Once Daily</td>
<td>Once daily for all indications</td>
<td>Treatment (continuous drip)</td>
</tr>
<tr>
<td><strong>Clearance</strong></td>
<td>Hepatic &amp; Reticulo-Endothelial System No renal adjustments</td>
<td>Renal Adjust for CrCl &lt; 30 mL/min</td>
<td>No adjustment in Dalteparin</td>
<td>Renal Contraindicated in CrCl &lt; 30 mL/min</td>
</tr>
<tr>
<td><strong>Ability to Cause HIT</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Case Reports</td>
<td>No</td>
</tr>
<tr>
<td><strong>Use in HIT Treatment</strong></td>
<td>No</td>
<td>No</td>
<td>Currently under study</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Use in Patient with a History of HIT</strong></td>
<td>If &gt;100 days since HIT occurrence, consider a retrial</td>
<td>If &gt;100 days since HIT occurrence, consider a retrial</td>
<td>A reasonable option-more studies required</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ACT, activated clotting time; aPTT, activated partial thromboplastin time; AT, antithrombin; BID, twice daily; LMWH, low molecular weight heparin; HIT, heparin-induced thrombocytopenia; UFH, unfractionated heparin.
UFH, a heterogeneous drug with a half-life of 45 to 90 minutes, has been the traditional choice for acute anticoagulation. Used subcutaneously in fixed doses for thromboembolism prophylaxis (5,000 to 8,000 units), the aPTT usually remains unaffected, and bleeding is very rare unless marked HIT occurs. Dosing every 8 hours is of proven effectiveness.

When UFH is used for full “therapeutic” anticoagulation, the goal is to promptly prolong the aPTT to 1.5 to 2 times the control value. (Either the patient's baseline aPTT or the midpoint of the laboratory normal range may be targeted.) Failure to achieve this goal within the first day is associated with an increased risk of clot extension and recurrent embolism. The best method of rapidly achieving and maintaining the therapeutic goal is to use one of several validated heparin dosing protocols. To achieve prompt success, UFH demands starting treatment with a bolus of heparin (≥80 units/kg) and an initial hourly infusion of ≥18 units/kg. However, even when using a dosing protocol, underanticoagulation and over-anticoagulation occur all too frequently. Many centers are replacing the aPTT with the more focused anti-factor Xa level to titrate UFH therapy or using this test together with the aPTT.

Despite little evidence to suggest anything more than weak correlation between aPTT values between 1.5 and 3 times control and bleeding tendency, physicians have strong fears of anticoagulation-induced bleeding. However, if the PT or aPTT is “infinitely” prolonged (>100 seconds), the tendency for unprovoked bleeding is decidedly increased. Because UFH inhibits the action of thrombin and factor Xa, in high doses, it can prolong the PT as well as the aPTT. The therapy of UFH overdose includes discontinuation of the drug, and in the hemorrhaging patient, administration of protamine sulfate (1 mg/100 units of circulating heparin). Except following cardiopulmonary bypass, protamine is rarely given in practice because of safety concerns and the difficulty in knowing how much should be administered.

Underdosing UFH is a more common error than administering an excess. In patients with active thrombosis, larger doses than those commonly used may be required to interrupt clotting. Unfortunately, there is no way to standardize the “clot burden” to guide therapy. The most common error in UFH dosing is failure to administer an adequate heparin bolus and increase the rate of infusion for patients with subtherapeutic aPTTs. Failure to rebolus and increase infusion rates results in an aPTT in the therapeutic range only 50% to 60% of the time. When a “high” aPTT is encountered, physicians often discontinue UFH infusions for extended periods of time, the result being subtherapeutic anticoagulation when next measured. In most cases, prolongation of the aPTT to more than twice control does not require interruption of UFH infusion, but merely reducing the infusion rate by 20% to 25%. Interruption of a continuous infusion of UFH for more than 2 to 3 hours will almost always result in a subtherapeutic aPTT, except in the setting of massive overdosage. (It obviously makes sense to interrupt administration in a bleeding patient.)

Overall, HIT develops in up to 20% of hospitalized patients given heparin, but most cases are those of the clinically insignificant nonimmune “type I.” The much more serious type II HIT is induced by the formation of antibodies to heparin that cross-react with platelet surface antigens. The syndrome may occur at any time during heparin therapy and has been reported in patients only receiving subcutaneous dosing or the tiny amounts infused in the maintenance of continuously flushing vascular access catheters. However, type II HIT rarely manifests before 7 days of heparin therapy in unsensitized patients and is most common in patients receiving higher doses. The incidence of both varieties of HIT is reduced but not eliminated by using LMWH. The most serious complication of HIT is not bleeding but thrombosis. Up to 50% of patients developing type II HIT experience thrombosis, the “white clot syndrome” of diffuse venous and arterial thrombosis induced by platelet aggregation. The development of thrombosis is associated with a mortality rate as high as 25%. Treatment of HIT should include discontinuing heparin and starting an alternate method of anticoagulation (e.g., a direct thrombin inhibitor). Platelet transfusions should be avoided. Among patients developing HIT, future heparin exposure should be avoided if at all possible; however, if unavoidable, waiting until PF4 antibody levels are undetectable and minimizing the duration of exposure may be the safest course of action.
LMWHs are AT activators purified from UFH. Low endothelial uptake and serum protein binding allow high bioavailability and slower clearance. The result is that appropriate doses of intermittent subcutaneous LMWH can be used for thromboembolism prophylaxis or treatment. Minor interactions of LMWH with vWF produce fewer platelet inhibitory actions than UFH and may account for the lower incidence of hemorrhage observed when using LMWH. LMWHs also have a lower incidence of HIT than UFH. The safety and efficacy of LMWH for treatment of thromboembolism in and out of the hospital have been clearly demonstrated. Outpatient therapy is also associated with significant reductions in cost.

All forms of heparin are cleared at least in part by the kidney. Hence, significant reductions in glomerular filtration rate (i.e., GFR < 30 mL/min) necessitate reducing doses for both prophylaxis and treatment. Unfortunately, there are no solid guidelines on how to modify prophylactic doses of UFH, but with regard to one LMWH, enoxaparin, one study indicates dose reduction from 40 to 30 mg per day is probably appropriate for most average-sized patients. With regard to therapeutic dosing in renal insufficiency, three choices exist: (1) use of UFH and monitoring of aPTTs, (2) use of reduced doses (1 mg/kg daily) of enoxaparin (the sole LMWH with published guidelines), or (3) empiric use of a LMWH and monitoring anti-Xa activity levels. Uncertainty continues regarding how to treat morbidly obese patients with heparins (see Chapter 23). In this setting, checking anti-Xa activity levels is probably prudent to avoid under- or over-anticoagulation.

**Fondaparinux, Argatroban, and Bivalirudin (Table 30-6)**

Fondaparinux is a synthetic pentasaccharide inhibitor of factor Xa. Weight-based dosing is used for prevention and treatment of thromboembolic disease. The purported advantage of fondaparinux, avoidance of HIT, is now in question with reports of an association between the drug and PF4 antibody formation. Significant limitations to use of fondaparinux are lack of a reversing agent and exclusively renal clearance. Because fondaparinux is cleared by the kidney and has a half-life of 17 to 20 hours even in patients with normal renal function, it should not be used in patients with renal insufficiency. Recombinant activated factor VII should be considered for critical bleeding with fondaparinux. Argatroban is a direct thrombin inhibitor used with percutaneous coronary procedures and in the setting of HIT. Monitoring is typically with an aPTT protocol or ACT in the cardiac suite. No specific reversal agents exist. If urgent bleeding is identified, FFP and a PCC may be considered. Bivalirudin is an agent with direct antithrombin effects. Clearance comes largely by proteolysis by thrombin (80%) with 20% renal excretion. There is no specific antidote. Hemodialysis, hemofiltration, or plasmapheresis should be considered for critical bleeding. Half-life is only 25 minutes with normal renal function and 1 hour in renal failure. Bivalirudin is rarely used in contemporary ICU practice. It is made to be given with aspirin and, if used, is employed with percutaneous coronary procedures.

**Warfarin (Table 30-7)**

Warfarin inhibits production of vitamin K-dependent proteins (II, VII, IX, X) prolonging the PT to a greater degree than the aPTT. The intensity and duration of warfarin anticoagulation should be guided by the severity of the thrombotic consequences. Because of interlaboratory variation in testing procedures, most hospitals now report the PT and an “international normalized ratio” (INR). INR reporting permits comparison of the intensity of warfarin anticoagulation among hospitals. The goal of warfarin therapy in thromboembolism has traditionally been to maintain PT 1.5 to 2.5 times the patient’s baseline or laboratory control. More intense anticoagulation has been advocated for patients with mural cardiac thrombi and mechanical prosthetic heart valves. However, evidence suggests that PT values 1.25 to 1.5 times control (INR 2 to 3) are adequate for most conditions, and less intense anticoagulation may lower hemorrhage risk.

Changes in previously stable INRs may result from dietary variation or administration of gutaltering antibiotics. Often, however, changes result from fluctuations in warfarin metabolism or protein binding induced by the addition or discontinuation of other drugs (e.g., erythromycin, phenobarbital, and phenytoin). Anticoagulation intensity is also increased by drugs that compete with warfarin for albumin binding (sulfas, sulfonarylureas, indomethacin, and
phenylbutazone). In patients with warfarin-induced bleeding and firm indications for chronic anticoagulation (i.e., prosthetic heart valves, recurrent embolism), interruption of warfarin for 2 to 4 days is usually uneventful. If more precise control of anticoagulation is needed, UFH or LMWH may be temporarily substituted. Vitamin K is usually sufficient to reverse the anticoagulant effect of warfarin in patients with an excessively prolonged PT without bleeding. However, vitamin K does not provide ideal reversal because its effect may be delayed 6 to 24 hours, and reanticoagulation may be difficult if more than 1 mg of vitamin K is given. In more urgent cases, (e.g., an invasive procedure), FFP or a PCC will promptly (but temporarily) reverse anticoagulation. During the initial days of conversion from intravenous heparin to warfarin, simultaneous use of both agents is advisable.

<table>
<thead>
<tr>
<th>Table 30-7. Direct Oral Anticoagulant Agents</th>
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<tbody>
<tr>
<td><strong>Warfarin</strong></td>
</tr>
<tr>
<td>Action</td>
</tr>
<tr>
<td>Peak action</td>
</tr>
<tr>
<td>Half-life</td>
</tr>
<tr>
<td>Renal elimination</td>
</tr>
<tr>
<td>PT/INR to goal (depending on condition)</td>
</tr>
<tr>
<td>aPTT</td>
</tr>
<tr>
<td>TT</td>
</tr>
<tr>
<td>ECT</td>
</tr>
<tr>
<td>Anti-Xa</td>
</tr>
<tr>
<td>Reversal strategy</td>
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</tbody>
</table>
Urgent reversal of warfarin effect is frequently required for patients who experience major bleeding or require urgent surgery. Treatment options include a combination of vitamin K and coagulation factor replacement with either a PCC or FFP, which obligates a greater intravascular fluid load. Recent reviews associate the use of PCC with a reduction in all-cause mortality compared to FFP. PCC use was more likely to achieve normalization of the INR and resulted in a shorter time to INR correction. Patients receiving a PCC also have a lower risk of posttransfusion volume overload compared to FFP. There appears to be little difference between PCC and FFP regarding the risk of thromboembolism following their administration.

Skin necrosis is a rare complication of warfarin anticoagulation traditionally associated with use of “loading doses,” especially when given to patients not receiving concurrent AT therapy (i.e., UFH, LMWH). Warfarin-induced necrosis is most likely to occur in patients with hereditary or acquired protein C deficiency and those with HIT. Pathologically, the mechanism of necrosis is the formation of microvascular thrombi, suggesting that necrosis is the result of inhibiting production of the anticlotting vitamin K-dependent proteins C and S.

**Direct Oral Anticoagulant Agents (Table 30-7)**

The most common indication for oral anticoagulation is reduction of stroke risk in atrial fibrillation. Warfarin has been the standard therapy for prevention of stroke in atrial fibrillation since its introduction in 1954. Difficulty of achieving consistent therapeutic dosing and bleeding risks associated with warfarin therapy has led to efforts to develop direct oral anticoagulant agents with improved efficacy and safety. Recently introduced agents include rivaroxaban, apixaban, edoxaban, and dabigatran. These agents are rapidly replacing warfarin in the prevention of thromboembolic events in patients with atrial fibrillation. Unlike warfarin, which acts on the vitamin K-dependent factors (II, VII, IX, and X), these newer agents target specific steps in the coagulation cascade. This targeted approach results in a more favorable pharmacokinetic response, eliminating the need for routine anticoagulant monitoring and allowing prescription of standard doses. Rivaroxaban, apixaban, and edoxaban are inhibitors of activated factor X, which is a primary regulating step in the coagulation cascade. Dabigatran is a direct thrombin inhibitor acting specifically within the coagulation cascade at the point where fibrinogen is converted into fibrin. These new oral anticoagulants are effective in reducing ischemic strokes associated with atrial fibrillation. However, the most significant benefit of these drugs is reduction of hemorrhagic strokes complicating anticoagulation therapy. There is also a reduction of spontaneous intracerebral hemorrhage. A major concern regarding use of this new class of agents in the emergent setting has been lack of reversal agents. Each of these drugs has a half-life between 8 and 15 hours, and their use may complicate management in the setting of acute injury and increase bleeding risk for emergent surgical procedures.

Four-factor PCCs have the potential to reverse bleeding because of warfarin or direct oral anticoagulant therapy. Their efficacy is based on their ability to increase levels of factors II, VII, and IX, and X. PCCs are often recommended in the setting of lifethreatening bleeding. At present, there are insufficient data to definitively conclude that reversing the direct oral anticoagulant effect (judged by standard laboratory tests) correlates with improved clinical outcomes. Recombinant factor VIIa is only partially effective for reversing of direct oral anticoagulant agents in experimental models and could increase thrombotic risk relative to PCCs. At present, only dabigatran has an approved reversal agent. Several agents are in development for specific reversal of direct oral anticoagulant activity.
**Table 30-8. Identified Hypercoagulable Disorders**

<table>
<thead>
<tr>
<th>Hypercoagulable Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated protein C resistance (factor V Leiden)</td>
</tr>
<tr>
<td>Prothrombin 20210 mutation</td>
</tr>
<tr>
<td>Protein C deficiency</td>
</tr>
<tr>
<td>Protein S deficiency</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
</tr>
<tr>
<td>Anticardiolipin antibody</td>
</tr>
<tr>
<td>Dysfibrinogenemias</td>
</tr>
</tbody>
</table>

**HYPERCOAGULABLE DISORDERS**

Knowledge regarding hypercoagulable disorders, also called thrombophilias, is much less complete than that for bleeding disorders. Routinely available laboratory tests cannot reliably predict a thrombotic tendency, and the assays possibly useful to predict thrombotic tendency are expensive, prone to artifact, and not widely available. Even though 20% to 40% of patients with thrombotic episodes are at least heterozygous for the factor V Leiden (activated protein C [APC] resistance) or prothrombin 20210 mutations, most episodes of arterial and venous thromboses cannot be attributed to any inherited or acquired prothrombotic blood disorder. Most patients with a thrombotic event do, however, have predisposing risks such as stasis, vascular intimal damage, or inflammation. The most common identifiable hypercoagulable disorders are outlined in Table 30-8. Useful clinical clues to raise suspicion of an inherited or acquired thrombotic tendency are outlined in Table 30-9.

**Table 30-9. Clinical Clues to Hypercoagulable Disorders**

<table>
<thead>
<tr>
<th>Clinical Clues</th>
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<tbody>
<tr>
<td>Family history of thrombotic events (usually venous)</td>
</tr>
<tr>
<td>Thrombotic event at an early age</td>
</tr>
<tr>
<td>Thrombosis without identifiable risk factor</td>
</tr>
<tr>
<td>Recurrent clotting episodes</td>
</tr>
<tr>
<td>Thrombosis at unusual site (upper extremity)</td>
</tr>
<tr>
<td>Recurrent spontaneous abortions</td>
</tr>
</tbody>
</table>

**Inherited Thrombotic Disorders**

Deficient quantities or activities of three specific plasma proteins, AT, protein C, and protein S, have been linked to a thrombotic tendency. Even though these conditions have long been appreciated, they are dwarfed in frequency and importance by the factor V Leiden (APC resistance) and prothrombin 20210 mutations. Quantitative, genetic, and functional assays now exist for numerous mutations; however, testing is expensive and interpretation complicated. For example, levels of all these clotting proteins can be altered by liver disease, DIC, pregnancy, anticoagulation, or the occurrence of a thrombotic event not precipitated by the protein deficiency. Hence, the involvement of an expert hematologist in the evaluation of patients with a suspected prothrombotic disorder is prudent.

Unfortunately, there are no reliable clinical features to distinguish patients with thrombophilia from patients without heritable clotting disorders except perhaps a strong family history of thrombosis. When clotting occurs, DVT of the
leg appears to be the most likely event. Arterial thrombosis or visceral, cerebral, or upper extremity thromboses occur less often.

Substantial controversy exists about the wisdom of testing for thrombophilias. Factor V and prothrombin mutations are relatively common, whereas the risk of thrombosis in the absence of additional risk factors is quite low. Therefore, it does not make sense to test a broad population of asymptomatic patients. An impassioned argument is often made to test patients developing thrombosis who have few or no recognized risk factors for thromboembolism or those having a second or third clotting episode. Reasons for such an approach usually include “knowing” about future risk to the patient and relatives, but unfortunately, there is no consensus about what should be done for patients with thrombosis and a concurrent mutation versus those lacking one. In addition, it is already recommended that patients with a second or third clotting episode receive lifelong anticoagulation, mitigating the need for diagnosis. The idea that asymptomatic family members should be tested at first blush appears to make sense, but the decision is complicated. First, most affected individuals do not experience thrombotic episodes unless additional risk factors are superimposed. Thus, lifelong prophylactic anticoagulation for asymptomatic carriers is not indicated and may confer substantial bleeding risk. Second, knowing that a relative has a mutation is not required to administer prophylaxis when additional risk factors develop (e.g., trauma, surgery, immobilization). Finally, diagnosing thrombophilia in an asymptomatic individual can have devastating unintended consequences for insurability, employment, and reproductive choices. Hence, consultation with a genetic counselor before testing is wise. If after careful consideration testing is believed to be indicated, first steps in the evaluation of patients with a suspected clotting disorder include testing for factor V Leiden, prothrombin 20210, AT, and proteins C and S.

**Factor V Leiden**

Factor V Leiden is the most prevalent thrombophilia. Although as much as 6% of the White population may be heterozygous for the disorder, the condition is substantially less prevalent among peoples of Native American, Hispanic, African, or Asian ancestry. The most common defect, a single amino acid substitution, renders factor V resistant to the neutralizing effects of APC. The genetic assay offers the advantage that it can be performed in patients with active thrombosis or those receiving anticoagulant therapy. Despite its frequency, the risk of thrombosis associated with the factor V mutation is substantially less than that for a person with protein C, S, or AT deficiency. Homozygotes are rare, and most thromboses occur among heterozygotes with multiple conventional risk factors.

**Prothrombin Gene Mutation**

A mutation at nucleotide pair 20210 in the gene coding for prothrombin is the second most common thrombophilia. The transformation is associated with an increase in circulating protein levels of about 30%. Like factor V Leiden, this mutation is very rare in patients of Asian or African descent, but can be found in up to 7% of Whites. Alone, the prothrombin mutation is believed to increase the risk of clotting three- to fourfold, but when it coexists with the factor V mutation, thromboembolism risk may be 20-fold higher than in individuals without either defect. Patients with the mutation cannot be detected merely by measuring the plasma prothrombin levels because substantial overlap exists with normals; genotyping is necessary for diagnosis.

**Antithrombin Deficiency**

AT, formerly known as antithrombin III, is a naturally occurring serine protease plasma anticoagulant that acts to inhibit the action of activated factors IX, X, and XI, and, most importantly, thrombin. The rate at which AT inactivates thrombin is dramatically increased (up to 10,000-fold) by the addition of heparin. AT deficiency is usually inherited as an autosomal dominant trait, with somewhere between 1 in 2,000 and 1 in 5,000 heterozygous for the protein. Heterozygotes are at increased risk for thromboses. Deficient homozygotes have not been identified, suggesting that such a severe deficiency is lethal. Spontaneous mutations (acquired disease) have rarely been described, and pregnancy, liver disease, DIC, nephrotic syndrome, and acute thromboses have been reported to reduce AT levels in genetically normal persons. Clinically, the disorder is usually suspected when the deficient protein renders patients
with clot resistant to the effects of heparin. Two general types of AT deficiency have been identified: reductions in plasma protein level or activity. The most common form of the disorder is a combined reduction in plasma protein level and functional activity. Normal AT levels with decreased functional activity represent the next most common form of the disorder. Immunological assays can measure the protein level, but functional assays are usually required to quantitate protein anticoagulant activity in the absence of heparin (progressive assay) or in the presence of heparin (heparin cofactor assay). An AT concentrate is now available for treatment of deficient patients; however, the mainstay of therapy remains lifelong anticoagulation for patients with demonstrated thrombotic events and AT deficiency.

**Protein C Deficiency**

The clinical presentation of protein C deficiency, a thrombin-activated vitamin K-dependent serine protease, is similar to that of AT deficiency. APC inhibits the activity of factors VIIIa and Va and increases fibrinolytic activity. As many as 1 in 200 persons in the general population is heterozygous for this autosomal dominant inherited condition and exhibits partial deficiency. Protein C levels can also be reduced by liver disease, DIC, use of chemotherapy, or the occurrence of acute thromboses. Warfarin reduces protein C and S levels, making laboratory determinations during therapy unreliable. Submaximal function of the enzyme may also result even when levels are normal. The importance of protein C deficiency is less certain than that for AT; most patients with reduced protein C levels are asymptomatic. Therapy for protein C deficiency includes chronic warfarin initiated during antithrombin coverage. Purified protein C and APC infusions are available. Although rare, skin necrosis has been associated with the institution of warfarin without concomitant heparin and when loading doses are used.

**Protein S Deficiency**

Protein S, another vitamin K-dependent protein, complexes with APC to potentiate its anticoagulant effect. Although protein assays for protein S exist, the free protein fraction is difficult to measure reliably. The most common form of protein S deficiency is a decrease in total level, though disorders in which the functional activity is decreased with normal total activity have also been described. Therapy for protein S deficiency is warfarin anticoagulation begun during heparin bridging.

**Lupus Anticoagulant/Antiphospholipid (Anticardiolipin) Antibody**

APLA is an IgG antibody directed against cardiolipin phospholipid that presents substantial risks for thrombosis and spontaneous abortion. Antibody titer correlates with the risk for thrombosis. APLA should be suspected in an appropriate clinical setting when the baseline aPTT is prolonged, especially if the platelet count is low. APLA can be confirmed using a factor Xa assay, a kaolin-activated aPTT, a dilute Russell viper venom time, or a dilute onestage PT. Alternatively, direct measurement of antibody titer can be performed. Therapy for patients with APLA syndrome includes higher-intensity warfarin anticoagulation.

**SUGGESTED READINGS**


Chapter 31
Hepatic Failure

• Key Points

1. Only hepatic failure caused by acetaminophen has an effective specific therapy; therefore, supportive care is the basis for treating most patients. In selected cases, transplantation may be an option.

2. Altered mental status in patients with hepatic failure frequently has a second treatable cause that is not hepatic encephalopathy (e.g., hypoglycemia, sepsis, increased intracranial pressure, medications, or recreational drug use).

3. Loss of hepatic function impairs immunocompetence to such a degree that infection is a major killer. Primary bacteremias and spontaneous bacterial peritonitis are common and should be a constant concern.

4. Intravascular volume is often normal or depleted despite total body fluid overload in patients with acute hepatic failure. Therefore, hemodynamic and renal status is often tenuous in these patients.

5. Loss of hepatic drug-detoxifying capacity radically alters the pharmacokinetics of most medications. Drugs, doses, and schedules must be reconsidered carefully, and drugs metabolized extensively by the liver should be avoided.

6. Because of the central role of the liver in maintaining hemostasis, hepatic failure often is complicated by bleeding, commonly from the GI tract.

CLASSIFICATION

Hepatic failure can arise as a primary process in a previously healthy person (e.g., acetaminophen overdose, acute viral hepatitis), through the progression of a chronic liver disease (e.g., cirrhosis, chronic viral hepatitis), or as part of the multiorgan failure syndrome. Whatever the cause, key manifestations are shared as one or more of the five major functions of the liver are disrupted: (1) maintenance of acid-base balance through lactate metabolism, (2) detoxification, (3) glucose and lipid metabolism, (4) protein synthesis (including clotting factors and albumin), and (5) phagocytic clearance of organisms and circulating debris. Hepatic failure has many remote organ manifestations with associated critical care implications (Fig. 31-1).

The classification of hepatic failure can be confusing. A three-tiered categorization of acute hepatic failure (AHF) is based upon the pace of progression to encephalopathy from the onset of jaundice: hyperacute developing in less than a week, acute evolving over 1 to 4 weeks, and subacute occurring over 5 to 26 weeks. This system has some utility for determining likely etiology and predicting outcomes but is not clearly superior to the traditional designation fulminant hepatic failure defined as the development of encephalopathy within 8 weeks of onset of symptoms. For simplicity, the general term AHF will be used in this chapter. Chronic liver disease present for more than 6 months will be discussed separately because of the vastly different spectrum of complications.

ACUTE HEPATIC FAILURE

Clinical Features

The diagnosis of AHF cannot be made until coagulopathy and central nervous system (CNS) dysfunction (encephalopathy) are present. Irritability, confusion, and vomiting are all early signs of CNS involvement. The
rate of progression of encephalopathy can be astonishing, with patients evolving from normal mental status to obtundation within hours. Fever is common early in the course, whereas hypothermia is more frequent later. The patient with AHF is typically tremulous and hyperventilating; “liver flap” (asterixis) and sustained clonus often can be elicited. Hypoxemia is present in most patients, and acute lung injury (ALI) complicates about one third of all cases. Although ascites and peripheral edema may occur in AHF, these signs result from portal hypertension and hypoalbuminemia, making them much more common among patients with chronic liver disease.

**Laboratory Features**

Leukocytosis with neutrophilia and transaminase elevation usually are present in AHF. Marked hyperbilirubinemia commonly precedes a fall in albumin and a prolongation of the prothrombin time (PT). Extensive hepatocyte destruction may impair glycogen storage and gluconeogenesis, giving rise to hypoglycemia. Low-grade disseminated intravascular coagulation (DIC) commonly results from decreased synthesis of clotting factors, together with failure of the liver to clear fibrin degradation products. In the absence of a pre-existing coagulopathy, deficient hepatic production of antithrombin proteins predisposes to thrombosis. In AHF with hepatic encephalopathy, ammonia concentrations usually are elevated; a normal value may help to exclude the diagnosis. That said, ammonia levels may be surprisingly low in patients with severe protein depletion. Furthermore, the degree of ammonia elevation correlates so poorly with changes in clinical status as
to limit its utility for following a patient's progress.

**Etiology**

AHF has a wide variety of causes (Table 31-1). However, approximately 50% of cases are proven to result from acetaminophen toxicity (see Chapter 33), and sophisticated testing reveals that a substantial proportion of cases previously classified as "indeterminate" (the second most common etiologic category) are likely acetaminophen related. The third most common cause is viral infection.

<table>
<thead>
<tr>
<th>Causes of AHF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections</strong></td>
</tr>
<tr>
<td><strong>Viral</strong></td>
</tr>
<tr>
<td>Hepatitis A, B, C, D, E</td>
</tr>
<tr>
<td>Adenovirus</td>
</tr>
<tr>
<td>Varicella zoster</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Epstein-Barr</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td><strong>Drug/Toxins</strong></td>
</tr>
<tr>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Tetracycline</td>
</tr>
<tr>
<td>Isoniazid</td>
</tr>
<tr>
<td>Rifampin</td>
</tr>
<tr>
<td>Phenytoin</td>
</tr>
<tr>
<td>Methylldopa</td>
</tr>
<tr>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Valproic acid</td>
</tr>
<tr>
<td>Anabolic steroids</td>
</tr>
<tr>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Halogenated anesthetics</td>
</tr>
<tr>
<td>Amanita phalloides mushrooms</td>
</tr>
<tr>
<td>Vitamin A</td>
</tr>
<tr>
<td>Herbal remedies</td>
</tr>
<tr>
<td><strong>Chemical hepatotoxins</strong></td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
</tr>
<tr>
<td>Benzene</td>
</tr>
<tr>
<td>Ethylene glycol</td>
</tr>
<tr>
<td>Ethanol</td>
</tr>
<tr>
<td>Phosphorus</td>
</tr>
</tbody>
</table>
Acetaminophen

Acetaminophen is safe when taken in recommended doses, but ingestion of as little as 6 g may be fatal. (Usually, a fatal dose exceeds 140 mg/kg.) Toxicity is most likely to occur among patients with chronic liver disease, those abusing alcohol, and patients receiving medications, which induce the cytochrome P450 system. Although most cases of AHF involve acetaminophen ingestion that exceeds 10 g/d, significant liver injury can occur with doses as low as 3 g/d. When adjusted for body weight, the approximate minimum dose of acetaminophen that can cause serious liver damage appears to be in the range of 125 mg/kg. Because acetaminophen is rapidly absorbed and usually quickly metabolized, most AHF patients will have low or undetectable acetaminophen levels at presentation. After ingestion of a toxic dose, symptoms are minimal for the first day, with the exception of nausea and vomiting. One to two days later, deteriorating liver function tests, right upper quadrant pain, and oliguria (because of antidiuretic hormone-like effects) become evident. At this time, transaminases may peak in the tens of thousands of units. Within 3 to 5 days, a rising bilirubin and PT are seen as hepatic transaminases and albumin decline. In this most advanced stage, mental status may decline and renal failure develop. If the patient is to spontaneously recover, improvement is typically noted between days 5 and 7. Of all causes, acetaminophen-induced AHF has the highest rate of spontaneous recovery, but predicting who will recover and who will die without transplantation is difficult. Poor prognostic factors are late presentation and the presence of coagulopathy, metabolic acidosis, renal failure, and cerebral edema.

When the time of ingestion is known, the risk of toxicity from an isolated acute acetaminophen ingestion may be predicted from the Rumack-Matthew nomogram. (Concentrations > 140 mg/dL ≥4 hours are predictive of toxicity.) Unfortunately, the time of ingestion is rarely certain, and patients with chronic exposure, pre-existing liver disease, or significant alcohol use may develop toxicity at much lower concentrations than the nomogram predicts. For these reasons, it makes sense to administer N-acetylcysteine (NAC) as quickly as possible to AHF victims unless certain acetaminophen is not the cause. NAC may retain effectiveness for up to 72 hours following acetaminophen ingestion. NAC protects by directly binding the toxic acetaminophen metabolites and repleting intracellular glutathione. Historically, an oral loading dose of 140 mg/kg followed by 17 additional doses of 70 mg/kg at 4-hour intervals has been used. Vomiting is a common problem with oral NAC protocols. Prophylactic antiemetics are often given. There are a number of intravenous NAC protocols. Intravenous NAC has anaphylactic risk similar to other drugs but is far better tolerated than oral consumption of NAC. A simple intravenous protocol includes a 4-hour infusion of NAC of 50 mg/kg/h followed by a 16-hour infusion at 6.25 mg/kg of NAC per hour. Both oral and intravenous NAC are effective and acceptable. Intravenous NAC is
favored in patients with vomiting or other contraindications to oral administration and documented hepatic failure. NAC may be discontinued with resolution of encephalopathy and coagulopathy (INR < 1.5).

**Viral Hepatitis**

The risk of developing AHF from viral hepatitis is small (<1%), but because viral infection is common, they collectively represent the third most common cause of AHF. Numerous agents including hepatitis A to E, Epstein-Barr virus, and cytomegalovirus can cause severe hepatitis. Hepatitis B and C account for more than 90% of cases, with hepatitis A contributing another 5%. Hepatitis B and C are transmitted predominantly through the exchange of body fluids (e.g., transfusion, needle stick, or sexual intercourse). Although blood transfer represents the highest relative risk, saliva and semen are also vehicles. Hepatitis B immunization, testing the donated blood supply and evaluating the liver function tests of donors, has dramatically reduced the risk of transfusion-induced disease. After exposure to the hepatitis B virus, a 2- to 3-month incubation period passes as the virus proliferates. During this time, viral surface antigen (HbsAg) can be detected in the serum of infected patients. Nonspecific, gastrointestinal (GI), systemic, and rheumatologic symptoms precede the onset of jaundice and elevation in liver transaminases, and in most patients, HbsAg disappears. In a small minority of patients, HbsAg persists in the circulation, signifying the presence of ongoing, chronic disease and high infectivity. Antibodies to the core antigen appear in the serum during the incubation period and are typically present for several months after the illness resolves. Antibodies to HbsAg develop during the period of convalescence and may persist for years. Most patients do not require treatment for acute hepatitis B infection, and the value of antivirals or interferon therapy for patients with hepatitis B-induced AHF is debated. The delta agent, or hepatitis D, may create disease by coinfecting or superinfecting patients with hepatitis B, producing a highly lethal combination.

In contrast to hepatitis B, hepatitis C is more likely to be clinically subtle in its initial stages and is a rare cause of AHF. Jaundice is uncommon with the acute illness and, when it does occur, is mild. Despite mild initial illness, hepatitis C is a major cause of chronic liver disease and cirrhosis. Even though 40% of infected individuals clear the virus spontaneously, if persistent infection is discovered, treatment with interferon alpha and antivirals accelerates viral clearance. Different genotypes of the virus have differential response rates, and treatment is complex, expensive, and side effect laden; consultation with a hepatologist is prudent. Because coinfection is common, patients diagnosed with hepatitis C should be tested for HIV and vice versa.

Hepatitis A and E differ in many respects from hepatitis B or C. Both hepatitis A and E are acquired by the fecal-oral route and often produce asymptomatic infection, especially in children. (Adults often are more symptomatic.) After ingestion, an average incubation period of a month precedes the onset of nonspecific constitutional and GI symptoms. In some patients, an icteric phase follows, which is associated with abnormalities of transaminases and coincides with the appearance of IgM antibodies. Fortunately, hepatitis A and E uncommonly are associated with either AHF or chronic infection. The exception to this rule may be pregnant women who appear to be more severely affected by hepatitis E (20% mortality).

Cytomegalovirus and Epstein-Barr virus are much less common causes of clinically important hepatitis and only rarely are associated with AHF.

**Ischemia**

Although ischemic AHF occurs only rarely as a primary process (e.g., Budd-Chiari, sickle cell crisis), life-threatening hepatic dysfunction often develops in patients with limited hepatic reserve when another insult tips the balance, even if minor. This injury can occur when nutritive flow is compromised by congestive heart failure or shock or when hepatocytes are damaged by circulating inflammatory mediators (e.g., severe sepsis) or severe hypoxemia.
Treatment

Initial Evaluation

Most patients with AHF should be cared for in an ICU because of their numerous physiologic problems and need for close monitoring (Table 31-2). Because AHF patients are complex and encouraging survival rates have been achieved with transplantation, potential candidates should be transferred early in their course to a facility with transplant capability and resources necessary to manage complications. Unfortunately, transplantation carries its own set of risks, and many good candidates die while waiting for a liver. Transplantation is best reserved for the otherwise healthy patient with isolated liver failure. For example, it clearly cannot benefit patients with metastatic carcinoma or those who have sustained irreversible brain damage from hypoxia, intracranial bleeding, or intracranial hypertension.

The first step after confirming respiratory and hemodynamic adequacy is to try to determine the etiology of AHF. An in-depth history should be obtained that includes medications (e.g., herbal remedies, vitamins, estrogens, acetaminophen), a dietary history targeting potential sources of hepatitis (e.g., travel, raw seafood consumption, and sick contacts), and hepatotoxin exposure (e.g., alcohol, carbon tetrachloride, mushrooms). Obviously, a detailed history of transfusion, needle sharing, and sexual activity is essential. A toxicological survey should be obtained that includes acetaminophen levels. A panel of serologic tests should be sent to search for viral causes listed in Table 31-1. Although rare in patients under 40, ceruloplasmin, serum copper, and a 24-hour urine for copper test should be sent to look for Wilson disease. Autoimmune hepatitis can be excluded by laboratory testing for antinuclear antibody, antimitochondrial antibody, and anti-smooth muscle antibody. A pregnancy test should be obtained in all women with childbearing potential. Basic laboratory studies including blood counts, bilirubin, transaminases, platelets, electrolytes, creatinine, arterial blood gases, and tests of hepatic synthetic function (albumin and PT) should be obtained. It is also reasonable to perform an ultrasound examination of the liver to evaluate its size, echogenicity, bile duct anatomy, and portal and hepatic vein patency and to look for ascites. In many cases, and essentially all cases where transplantation is a consideration, a contrasted abdominal computed tomography (CT) scan will be performed to evaluate liver and spleen size and texture and vascular anatomy. Obviously, the decision to administer contrast media should be well reasoned, given the risks of contrast-induced nephropathy. As initial data are being gathered, potential consultants (e.g., hepatologist, transplant surgeons, and neurosurgeons) should be contacted.

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Table 31-2. Common Management Issues and Condition-Specific Elements of Care in Acute Liver Management

<table>
<thead>
<tr>
<th>Organ System and Common Conditions</th>
<th>Assessment</th>
<th>Specific Elements of Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARDIOVASCULAR SYSTEM</td>
<td>Hypotension</td>
<td>Invasive monitoring, echocardiography</td>
</tr>
<tr>
<td>Intravascular volume depletion</td>
<td>Correction of volume depletion</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------</td>
<td>-------------------------------</td>
<td></td>
</tr>
<tr>
<td>Vasodilatation</td>
<td>Vasopressors</td>
<td></td>
</tr>
<tr>
<td>Low cardiac output and right ventricular failure</td>
<td>Inotropic support</td>
<td></td>
</tr>
</tbody>
</table>

**RESPIRATORY SYSTEM**

<table>
<thead>
<tr>
<th>Aspiration pneumonitis</th>
<th>Monitor level of consciousness</th>
<th>Early tracheal intubation</th>
</tr>
</thead>
</table>

**METABOLIC AND RENAL SYSTEMS**

<table>
<thead>
<tr>
<th>Hypoglycemia</th>
<th>Laboratory metabolic testing</th>
<th>Maintain normoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td></td>
<td>Active fluid management</td>
</tr>
<tr>
<td>Renal dysfunction, lactic acidosis, hyperammonemia</td>
<td></td>
<td>Renal-replacement therapy</td>
</tr>
<tr>
<td>Impaired drug metabolism</td>
<td></td>
<td>Review drug administration</td>
</tr>
</tbody>
</table>

**CENTRAL NERVOUS SYSTEM**

<table>
<thead>
<tr>
<th>Progressive encephalopathy</th>
<th>Neurologic observation; serum ammonia level; transcranial ultrasonography; intracranial-pressure monitoring</th>
<th>Treatment of fever and hyponatremia; screening for sepsis High-grade encephalopathy: endotracheal intubation; avoidance of $P_{aco_2}$ of $&lt;30$ mm Hg or $&gt;45$ mm Hg; target for serum sodium, 145-150 mmol/L; risk assessment for intracranial hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial hypertension</td>
<td></td>
<td>Interventions: osmotherapy (mannitol, hypertonic saline); temperature control</td>
</tr>
</tbody>
</table>
Supportive Care

Patients should be positioned with the head of the bed elevated to decrease the risks of aspiration and cerebral edema. Neurological status should be monitored frequently, typically every 1 to 2 hours. Prophylactic therapy for gastric ulceration should be undertaken. Special vigilance for hypoglycemia should be maintained because it is a common, potentially lethal, and easily treated cause of altered mental status. Supportive care includes maintenance of adequate nutrition and hemodynamic support as well as monitoring for the most frequent complications: (1) encephalopathy and cerebral edema, (2) infection, (3) coagulopathy and bleeding, and (4) renal failure.

N-Acetylcysteine

NAC is indicated for treatment of proven or suspected acetaminophen toxicity as described above. In addition, a randomized trial of NAC versus placebo for non-acetaminophen-induced AHF suggests a substantial survival benefit (52% vs. 30%) for patients with Grade I or II encephalopathy at the time treatment was started. Given the safety profile, cost, and ease of administration, a strong case can be made to administer NAC to Grade I and II AHF patients, regardless of etiology, while awaiting confirmatory trials.

Complications

Encephalopathy

The causes of encephalopathy in liver failure are poorly understood but almost certainly differ between patients with acute and chronic disease. Intracranial hypertension induced by cerebral edema is the most common cause of encephalopathy in AHF but seldom complicates chronic liver disease. A standardized grading system for encephalopathy is presented in Table 31-3. Even though cerebral edema is usually the cause of altered mental status, hypoglycemia, infection, electrolyte imbalance, drug toxicity, and hypoxemia cannot be overlooked. The risk of cerebral edema is proportional to the speed with which encephalopathy develops. This complication is a serious problem; many AHF deaths are attributable to cerebral edema. Young age and high arterial ammonia levels (>200 mmol/L) are associated with increased risk of death from herniation. Patients with chronic liver disease appear to be able to export other organic osmolar substances at a rate capable of offsetting this effect (probably because of lower rates of ammonia formation). Physical examination is rarely helpful in detecting cerebral edema, and even the head CT scan is relatively insensitive to this diagnosis. (The CT is helpful, however, in ruling out other potential causes of altered mental status like intracranial hemorrhage or metastatic disease.) To monitor intracranial pressure (ICP) accurately, an invasive monitor must be inserted. (See Chapter 34, Neurological Emergencies.) The decision to insert an ICP monitor is usually controversial because it necessitates sedation and intubation, and by the time the procedure is considered, essentially all patients have significant coagulopathy. Even though supportive data are lacking, understandably most neurosurgeons require a platelet count greater than 50,000 to consider doing the procedure.

PaCO\textsubscript{2} denotes partial pressure of arterial carbon dioxide.

than 50,000/mm$^3$ and a PT ≤ 1.5 times normal before monitor placement. (Normalizing the PT may require specialized coagulation factor concentrates or as many as 8 to 12 units of fresh frozen plasma [FFP].) The controversy over invasive monitoring is enhanced by the absence of data demonstrating improved outcomes. The intraparenchymal monitor offers the best balance between accuracy and safety and is the most commonly used ICP monitor in acute hepatic failure (AHF). If employed, the ICP monitor is typically inserted as patients enter stage III encephalopathy. Elevated ICP is rarely seen in patients with Grade I or Grade II encephalopathy.

**Table 31-3. Classification of Hepatic Encephalopathy**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>I</td>
<td>Behavioral alteration without change in level of consciousness</td>
</tr>
<tr>
<td>II</td>
<td>Disorientation, hallucinations, drowsiness, asterixis</td>
</tr>
<tr>
<td>III</td>
<td>Somnolent but arousable, confusion, incoherent speech</td>
</tr>
<tr>
<td>IVA</td>
<td>Unconscious but arousable</td>
</tr>
<tr>
<td>IVB</td>
<td>Unresponsive to pain</td>
</tr>
</tbody>
</table>

When invasive monitoring is used, maintaining the cerebral perfusion pressure (CPP), defined as the difference between the mean arterial pressure and ICP, greater than 60 to 80 mm Hg appears to be an important goal. CPP can be increased by raising mean arterial pressure with vasopressor and/or lowering ICP. Simple measures including elevation of the head of the bed to 30 degrees and avoiding excessive fluid administration, coughing, and Valsalva maneuvers can reduce ICP. Keeping the head midline and avoiding neck flexion prevent compromise of jugular vein outflow. Unfortunately, even when diagnosed, the elevated ICP of AHF often fails to respond to treatments effective for brain edema from other causes. Surgical decompression and dexamethasone are of no benefit. Hyperventilation (PaCO$_2$ 30 to 35 mm Hg) is only transiently helpful, and although mannitol (0.5 to 1 mg/kg every 6 hours) may temporarily reduce edema, there is little evidence that survival is increased. When mannitol is used, serum osmolarity should not exceed 310 to 320 mOsm. (Mannitol is not useful in patients who have developed oliguria because it cannot be excreted.) Hypertonic saline targeting a serum sodium of 145 to 155 may have value. In desperate situations, induction of a barbiturate coma using thiopental or pentobarbital may be considered. Deep sedation with propofol or barbiturates with or without paralysis may also reduce cerebral oxygen consumption and ICP. Moderate hypothermia, with a goal core temperature of 33°C to 34°C, may prevent or help control elevated ICP. Patients may be spontaneously hypothermic, or they may be made so by fluids or continuous renal replacement therapy (CRRT). Cooling blankets may further reduce core temperature. A continuous EEG can monitor for burst suppression, the primary goal used when inducing barbiturate coma. In the absence of ICP monitoring, the management of the AHF patient with advanced hepatic encephalopathy is largely empiric and often targets maintenance of mean arterial pressure above 80 mm Hg, based on the assumption that the ICP may be elevated to 20 mm Hg. In distinction to portosystemic encephalopathy (PSE) of chronic liver disease, lactulose offers little benefit for the encephalopathy of AHF.

**Infection**

Acute and chronic liver failures predispose to infection by decreasing opsonins, complement levels, and phagocytosis. Up to 80% of AHF victims develop bacterial infections and 30% of patients developed fungal
infections. Interestingly, fever and leukocytosis occur in a minority of cases during infection, and there is a surprisingly high rate of positive blood cultures despite few signs of infection. Pneumonia and urinary tract and catheter-related sepsis are common infections that are largely preventable if using good supportive care. Spontaneous bacterial peritonitis (SBP), which occurs commonly among patients with ascites from portal hypertension of chronic liver failure, is relatively uncommon in AHF. Avoiding serious infection is critical because it is life threatening in and of itself; moreover, development of serious infection almost always disqualifies the patient for transplantation. *Staphylococcus* and *Streptococcus*, followed by Gram-negative rods, are the predominant organisms. Randomized trials have shown prophylactic antimicrobials decrease the incidence of infection without altering mortality; nevertheless, antimicrobials are usually administered.

**Coagulation Disorders and Bleeding**

Coagulopathy is frequent in AHF because all clotting factors are produced by the liver, with the exception of factor VIII/von Willebrand factor (see Chapter 30). Failure to produce clotting factors results in elevation of the PT and activated partial thromboplastin time (aPTT). In addition, loss and dysfunction of Kupffer cells, which normally clear clot degradation products from the circulation, increase the risk of DIC. When thrombocytopenia occurs, it is usually because of DIC, often from infection. Interestingly, despite the high frequency of abnormal clotting studies, spontaneous bleeding is relatively uncommon. (When it occurs, gastritis and esophagitis are the most common sources.) This rarity of bleeding may be explained by the fact that the liver also produces anticoagulation factors (antithrombin and proteins C and S), which decline concurrently. Second, patients with AHF rarely have significant portal hypertension making variceal bleeding very rare.

Because there is a poor correlation between laboratory studies and spontaneous bleeding risk, routine correction of clotting tests is not warranted. Despite the absence of data to support correction of clotting studies before performing invasive procedures, it is almost always attempted, especially before ICP monitor insertion. Importantly, up to 25% of patients are vitamin K deficient, and doses of 10 mg/d safely augment production of factors II, VII, IX, and X when the liver retains residual synthetic function. Hence, vitamin K should be tried in most patients. When synthetic function is inadequate, FFP can be used to correct the PT before an invasive procedure is performed or to treat active bleeding. FFP is not routinely indicated for correction of abnormal clotting parameters because it presents a volume challenge that may increase ICP, risks infection and immunologic reactions, and obscures the ability to gauge the hepatic endogenous clotting factor production. Furthermore, prophylactic administration of FFP has been shown to not decrease bleeding risk. Another strategy to be considered is administration of activated recombinant factor VII, which can temporarily correct the international normalized ratio (INR). A minimum dose reported of 40 μg/kg is recommended to achieve transient reversal of coagulopathy with a therapeutic window of 60 to 90 minutes—often sufficient to perform an invasive procedure. A second dose of this product may be administered if necessary to achieve normalization of the INR.

Because fibrinogen is an acute-phase reactant produced by the liver, levels are unpredictable in AHF. In patients who are bleeding, measurement of fibrinogen is warranted if coagulation parameters are not normalized by FFP. When levels fall below 100 mg/dL, cryoprecipitate is the most effective fibrinogen replacement. There are no reliable data to guide platelet transfusions, but consensus suggests a transfusion threshold of 50,000/mm³.

**Acute Kidney Injury**

Acute kidney injury (AKI) develops in up to 75% of all patients with AHF, most commonly from the direct
toxicity of acetaminophen. When AKI occurs in patients with non-acetaminophen-induced AHF, hypotension from volume depletion and severe sepsis are the most common causes. Blood urea nitrogen (BUN) levels are not a reliable indicator of renal function in AHF because production of urea nitrogen by the liver is impaired. The diagnosis and therapy of AKI are outlined elsewhere (see Chapter 29).

**Nutrition**

Although sufficient calories and protein of high biologic value must be provided, high loads of protein should be avoided in AHF. Vitamin K, thiamine, and folate are required by most patients. Sufficient glucose should be given to prevent hypoglycemia and to provide protein-sparing effects (see Chapter 16). Branched-chain amino acids have not been shown to be superior to other formulations. Restoring a positive nitrogen balance is a major goal of nutritional repletion and may be assessed by standard tests of urine urea nitrogen. Indirect calorimetry should be used to predict energy requirements.

**Pulmonary Complications**

Aspiration, pneumonia, atelectasis, and abnormal ventilation-perfusion \((\text{V with dot above})/\text{(Q with dot above})\) matching all contribute to the frequent development of hypoxemia in patients with AHF. Acute \((\text{V with dot above})/\text{(Q with dot above})\) mismatching probably is due to failure of the damaged liver to clear vasodilating humoral substances. A reduced level of consciousness, abdominal distention, and splinting from pain caused by a swollen liver all can induce hypoxemia by atelectasis. Pulmonary edema because of fluid overload, hypoalbuminemia, impaired cardiac contractility, and increased vascular permeability all may occur. As patients enter stage III encephalopathy, most will require intubation and mechanical ventilation.

**Miscellaneous Complications**

Many liver-metabolized drugs pose lethal threats in AHF. Because narcotics, sedatives, and anesthetics severely depress mental status and glottic reflexes in these sensitive patients, indiscriminate use may be fatal; careful dosing and monitoring are mandatory. Long-acting sedatives given frequently or in large doses should be avoided because of cumulative drug effects. If sedation is necessary, small doses of short-acting drugs without active metabolites should be used. If neuromuscular blocking agents are used, those not requiring hepatic metabolism are favored (e.g., succinylcholine, pancuronium, and atracurium).

**Prognosis**

Outcome is determined largely by patient characteristics and the cause and severity of hepatic failure. Prognosis favors patients between the ages of 10 and 40 years. On the other hand, AHF caused by non-A or non-B hepatitis or drugs (exclusive of acetaminophen) tends to respond poorly. Similarly, development of coma, a bilirubin greater than 18 mg/dL, an arterial pH less than 7.30, an INR greater than 3.5, and less than 10% activity of any specific clotting factor are poor prognostic indicators. The occurrence of any other associated organ failure (e.g., ALI or AKI) also dramatically reduces the chances for survival. These factors have been amalgamated into a single index: the model for endstage liver disease (MELD) score calculated as 

\[ = 10 [0.957 \times \ln(\text{serum creatinine}) + 0.378 \times \ln(\text{serum bilirubin}) + 1.120 \times \ln(\text{INR}) + 0.643] \]

On-line MELD calculators are available. Hyponatremia has been shown to heighten risk for these patients and in recent years has been
incorporated into this risk predictor. In addition to quantifying severity for patients with liver disease, the modified MELD score has become a key quantitative standard for ranking transplant candidates.

**CHRONIC LIVER FAILURE**

**Etiology and Pathophysiology**

Alcoholism, chronic viral hepatitis (hepatitis B and C), and nonalcoholic steatohepatitis (NASH) are the most common causes of chronic liver failure and cirrhosis. In addition to loss of hepatic functions including metabolic processing and/or excretion of drugs and toxins, glucose and lipid metabolism, as well as synthesis of clotting factors and albumin, cirrhosis presents a unique mechanical problem—portal hypertension. As the cirrhotic liver shrinks from scarring, cephalad flow of blood from the portal to hepatic veins is blocked. Rising portal pressures cause blood to shunt around the liver through the lower-pressure vessels of the stomach, esophagus, abdominal wall, and rectum, gradually dilating these fragile vessels into varices and hemorrhoids. Elevated portal pressure also forms ascites and causes splenomegaly by increasing back pressure in the splenic vein.

**Clinical and Laboratory Features**

Thrombocytopenia occurs commonly as splenic dilation sequesters platelets and hepatically produced thrombopoiesis factors decline. The tendency for ascites formation is enhanced by hypoalbuminemia because of reduced albumin synthesis. When massive, ascites limits diaphragmatic excursion, encouraging atelectasis at the lung bases and increasing the work of breathing. Gynecomastia, spider telangiectasia, and palmar erythema are physical signs that probably relate to failure of the damaged liver to clear both estrogens and vasodilating humoral mediators. Impaired metabolic processing capacity from loss of hepatocytes typically results in a low BUN. Jaundice results from impaired bilirubin metabolism; ecchymosis stem from impaired coagulation factor synthesis, often manifest as a prolongation of the PT. Although the MELD score is now commonly used to describe severity of illness among patients with acutely decompensated liver failure, the older Child-Pugh criteria (Table 31-4) are often used to categorize patients with chronic liver disease.

| Table 31-4. Child-Pugh Classification of Chronic Liver Disease |
|---------------------------------|-----------------|-----------------|-----------------|
| **Parameter**                   | 1 Point         | 2 Points        | 3 Points        |
| Bilirubin                       | <2              | 2-3             | >3              |
| Albumin                         | >3.5            | 3.5-2.8         | <2.8            |
| International normalized ratio (INR) | <1.7           | 1.7-2.3         | >2.3            |
| Ascites                         | Absent          | Mild to moderate| Severe/refractory |
| Encephalopathy grade            | 0               | I-II            | III-IV          |
Hepatic encephalopathy, also known as PSE, is the most common cause of altered mental status in chronic liver disease, but it is important to exclude other more readily reversible causes of altered consciousness including (1) hypoglycemia, (2) infection (especially SBP), (3) electrolyte imbalance (e.g., hyponatremia), (4) drugs (particularly sedatives), (5) hypoxemia, and (6) thiamine deficiency. Hypoglycemia is important because it can cause permanent neural damage and is easily reversible. Likewise, thiamine deficiency is perilous but easily corrected.

PSE arises when cirrhosis causes shunting of toxin-laden portal blood around the liver into the systemic circulation. Ammonia, fatty acids, mercaptans, and other false neurotransmitters have been implicated as causative, but there is no clear consensus on etiology. Encephalopathy may produce focal neurological deficits as well as alterations in consciousness and cognition. In salvageable patients, mental status responds to appropriate therapy within several days. A standard grading system for encephalopathy is presented in Table 31-3.

Regardless of the specific mechanism, a number of factors can precipitate or worsen PSE. High protein intake or upper GI hemorrhage increases the protein load and toxin production. Intravascular volume depletion from bleeding or diuretic use worsens mental status by reducing hepatic and renal perfusion and predisposing patients to contraction alkalosis. In turn, alkalosis and hypokalemia increase ammonia production and impair its renal excretion, further worsening mental status. Excessive withdrawal of ascitic fluid may redistribute fluid from the vascular space to the peritoneal cavity, further decreasing hepatic perfusion. Because of the complications of hypovolemia, weight lost through the use of diuretics or fluid restriction usually should not exceed 1 to 2 lb/d. Failing renal function accentuates the accumulation of toxins. Almost any systemic infection may alter mental status, but the most common infection precipitating PSE is SBP. All drugs (but particularly sedatives and narcotics) must be used with extreme caution when hepatic metabolism is impaired.

The diagnosis of PSE is made on clinical grounds and can be supported by elevated blood ammonia levels (60% to 80% of patients) or specific electroencephalogram (EEG) findings. Although an EEG occasionally demonstrates characteristic abnormalities (high-amplitude δ and triphasic waves), unfortunately, the EEG usually shows only nonspecific, diffuse slowing. CT scanning of the brain can reveal intracranial hemorrhage or nonspecific cerebral edema but cannot confirm a diagnosis of hepatic encephalopathy. When there is concern for the possibility of meningitis, lumbar puncture should be performed. For patients with subtle encephalopathy or in cases where the diagnosis remains in doubt, a therapeutic trial of antibiotics should be undertaken after other causes of reversible encephalopathy are excluded. Response usually occurs within 3 to 4 days if the diagnosis is accurate. An approach to management of PSE is found in Figure 31-2.

Correction of precipitating causes (bleeding, drugs, infection, alkalosis, hypoxia, renal failure, hypoglycemia, constipation, hypovolemia) is key to improvement. Nutritional support should be maintained in PSE with protein administration amounts of 1.2 to 1.5 g/kg/d. Calorie support should be as high as 35 to 40 kcal/kg/d. Administration of branched-chain amino acids should be considered in protein-intolerant patients. Feedings—parenteral and perhaps enteral—that are relatively rich in branched-chain amino acids may help reduce the availability of aromatic amino acids, which act as precursors for the central neurotransmitters that alter neuronal excitability. Laxatives and enemas decrease fecal generation of nitrogenous toxins, but profuse or protracted diarrhea sufficient to cause fluid depletion and electrolyte abnormalities must be avoided. Lactulose, a synthetic nonabsorbable disaccharide, usually is the choice for reducing the intestinal burden.
of toxins. Lactulose is broken down by colonic bacteria to lactic and acetic acids, compounds that promote bowel stools transit. Initially, 15 to 30 mL is given every 6 hours, and then the dose is modified to produce three loose stools per day. As with other laxatives, excessive diarrhea may deplete intravascular volume, worsening hepatic encephalopathy and sometimes precipitating the hepatorenal syndrome (HRS). Rifaximin is a useful antibiotic supplement and/or alternative for the lactose unresponsive or intolerant patient. Neomycin, an older, poorly absorbed broad-spectrum antibiotic, is sometimes used. Because as much as 5% of the drug may be absorbed systemically, worsened renal insufficiency or ototoxicity may occur when large doses of neomycin are given to patients with pre-existing renal dysfunction. Vancomycin and metronidazole may also be considered.

**Ascites and Hepatic Hydrothorax**

Ascites frequently is present in chronic liver disease, and on occasion, a pleuroperitoneal communication may allow ascitic fluid to enter the chest, producing a symptomatic pleural effusion (hepatic hydrothorax). Although the natural tendency is to drain such pleural effusions, the positive pressure inside the ascites-filled abdomen acting in conjunction with negative pleural pressure typically refills the pleural space in hours to days. In this setting, it is important to avoid tube thoracostomy. Insertion of a chest tube often results in a never-ending flow of pleural fluid, which leads to protein and lymphocyte depletion. The development of ascites with or without pleural fluid may impair ventilation and increase the work of breathing. Usually, sodium and water restriction and diuretic therapy are sufficient to limit ascites to manageable levels. Spironolactone, a potassium-sparing diuretic, alone or in combination with a loop diuretic, usually is effective. When diuretics fail, large-volume paracentesis may temporarily improve gas exchange and patient comfort. Rarely, ascites can become so tense that venous return is impaired and urine flow declines—in essence, “abdominal tamponade,” also known as the abdominal compartment syndrome. The mechanism of reduced urine flow is uncertain but may be the result of decreased venous return or compression of renal veins or arteries. Regardless of mechanism, decompression of the abdomen by paracentesis before renal injury develops rapidly restores urine output. Removal of large volumes of ascites can, on occasion, precipitate hypotension, which responds to intravenous volume replacement. Controversy persists about the relative benefits of colloid and crystalloid in this situation.

**Spontaneous Bacterial Peritonitis**

SBP is a common complication of chronic liver disease in which bacteria seed the peritoneal cavity. Hypoperfusion often precipitates SBP, presumably by impairing mucosal and bowel wall integrity. For this reason, many clinicians routinely administer antibiotics to patients with cirrhosis and ascites who develop significant GI bleeding. In patients with ascites, sudden deterioration of renal function or mental status, rapid weight gain, and ascites that becomes resistant to diuretic therapy all should prompt consideration of SBP. Classically, SBP may be recognized by the triad of fever, abdominal pain, and encephalopathy. However, SBP differs from peritonitis of other causes (secondary peritonitis) in that fever, abdominal pain, and tenderness are often subtle. Approximately 25% of all patients with SBP have only extra-abdominal symptoms and 5% of patients are entirely asymptomatic.

Nothing short of obtaining peritoneal fluid can exclude the diagnosis of SBP. Table 31-5 contrasts the fluid characteristics of uninfected ascites with those of spontaneous and secondary peritonitis. An ascitic fluid pH less than 7.31, a gradient in pH between the serum and ascitic fluid of more than 0.1 units, or an ascitic fluid lactic acid level higher than 32 mg/dL is suggestive of infective peritonitis. Diagnosis is confirmed when bacteria are seen on Gram stain or grow in culture. An absolute neutrophil count in the ascitic fluid greater
than 250/mm³ should prompt empiric therapy, particularly if polymorphonuclear leukocytes predominate. In contrast to secondary peritonitis, which is typically polymicrobial, cultures in SBP usually grow only a single organism. Nonetheless, patients with SBP may have polymicrobial infections. The single most likely organism is *Escherichia coli*, but Gram-positive infections are not uncommon. Because bacteremia occurs in many cases, blood cultures should be obtained. A third-generation cephalosporin is an appropriate initial coverage for most patients. A typical initial course is 5 days. Antibiotics may be extended for patients who failed to respond to initial therapy.

**Hepatorenal Syndrome**

The HRS is a potentially lethal condition of uncertain cause, which is unique to patients with chronic liver disease. The diagnosis of HRS can be knotty because many HRS victims have experienced multiple potential renal insults including nephrotoxic drugs and intravascular volume depletion from undertreated GI hemorrhage, overzealous paracentesis, or excessive diuretic usage. HRS is characterized by increasing serum creatinine and oliguria, which fails to respond to fluids or diuretics. Because patients with chronic liver disease often have low muscle mass, initial rises in creatinine may seem unimpressive, delaying recognition. In addition, the calculated creatinine clearance overestimates renal function. Urinary Na⁺ values are typically very low (<10 mEq/L).

<table>
<thead>
<tr>
<th>Fluid Parameter</th>
<th>Benign Hepatic Ascites</th>
<th>Spontaneous Bacterial Peritonitis</th>
<th>Secondary Peritonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total leukocyte count (cells/mm³)</td>
<td>&lt;1,000</td>
<td>&lt;1,000</td>
<td>&gt;&gt;1,000</td>
</tr>
<tr>
<td>Neutrophil count (cells/mm³)</td>
<td>&lt;250</td>
<td>&gt;250</td>
<td>&gt;&gt;250</td>
</tr>
<tr>
<td>Culture</td>
<td>No growth</td>
<td>Single organism</td>
<td>Multiple organisms</td>
</tr>
<tr>
<td>Protein</td>
<td>Low</td>
<td>Low</td>
<td>&gt;1 g/dL</td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td>Normal</td>
<td>Normal</td>
<td>High</td>
</tr>
<tr>
<td>Glucose</td>
<td>Normal</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>pH</td>
<td>&gt;7.4</td>
<td>&lt;7.4</td>
<td>&lt;&lt;7.4</td>
</tr>
</tbody>
</table>

The definitive treatment is liver transplantation, but obviously not all patients are candidates, and delays in obtaining a donor organ necessitate an interim support plan. A significant number of cases of HRS respond to a therapeutic protocol that combines norepinephrine with albumin administration. Norepinephrine is given intravenously as a continuous infusion (0.5 to 3 mg/h) with the goal of raising mean arterial pressure by 10
to 15 mm Hg, and albumin is given for at least 2 days as an intravenous bolus (1 g/kg predicted weight per
day and 100 g maximum). Intravenous vasopressin, octreotide, and midodrine may also be employed with
titration upward as needed to raise mean arterial pressure. In patients failing to respond to medical therapy,
a transjugular intrahepatic portosystemic shunt (TIPS) may be considered. However, this procedure
requires contrast administration, which could injure the kidney and risk precipitating or worsening PSE.
Patients with HRS who progress to renal failure may be treated with dialysis, which is most commonly
undertaken when these

individuals are awaiting a liver transplant or there is a legitimate hope of eventual recovery of liver function.

**Gastrointestinal Bleeding**

The subject of GI bleeding is covered in depth in Chapter 37. Because GI bleeding frequently produces
shock, sepsis, hepatic encephalopathy, or hypoperfusion that initiates acute renal failure, it is often the
proximate cause of death in patients with *chronic* hepatic failure and portal hypertension. The most common
sources are gastritis and esophagitis, but patients with portal hypertension are predisposed to bleed from
esophageal varices. Coagulopathy frequently accentuates the tendency for GI blood loss. Histamine (H₂)
blockers and proton pump inhibitors are effective in preventing stress ulceration.

**SUGGESTED READINGS**


D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a

Ford RM, Sakaria SS, Subramanian RM. Critical care management of patients before liver transplantation.

Liao WC, Hou MC, Chang CJ, et al. Potential precipitating factors of esophageal variceal bleeding: a case-


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Chapter 32
Endocrine Disturbances in Critical Care

• Key Points

1. Critical illness and medical interventions disrupt intricately coordinated endocrine rhythms, which normally follow diurnal patterns and mediate homeostatic adjustments. In severe disease, body organs alter their normal sensitivities to hormonal controls of metabolism, with potentially adaptive or maladaptive consequences. Stage of illness plays a key role in determining cellular responsiveness as well as the amplitudes of neuroregulatory and metabolic endocrine drivers of endogenous response and recovery.

2. Severe hypothyroidism and hyperthyroidism must be suspected and treated on clinical grounds; laboratory tests, though helpful for confirmation, may be misleading and responses delayed or out of step with function. When beginning treatment for hypothyroidism, consideration must be given to concomitant adrenal insufficiency.

3. Endocrine disorders often have subtle presentations in the ICU. Altered mental status (diabetic ketoacidosis, hypothyroidism, and hyperthyroidism), failure to wean from mechanical ventilation (adrenal insufficiency and hypothyroidism), and refractory hypotension (adrenal insufficiency, diabetes insipidus) are the most common clinical presentations for which endocrinologic causes are overlooked.

4. When adrenal insufficiency is suspected, diagnostic investigation and institution of therapy (isotonic saline and corticosteroids) should be undertaken.

5. Because overt hyperglycemia holds damaging potential in varied forms of critical illness, glucose concentrations must be monitored and kept close to broad normal limits.

6. Interrupted feedings and long-acting insulin are preventable causes of hypoglycemia, an important and often subtle problem of the critically ill.

7. Ample fluid administration, low-dose insulin, and potassium replacement are fundamental to the care of diabetic ketoacidosis.

8. Because hypertonic glucose is partially responsible for maintaining the circulating volume in patients with hyperosmolar nonketotic coma, adequate volume resuscitation is essential before beginning insulin therapy.

9. Diabetes insipidus is suspected when large volumes of dilute urine are accompanied by hyperosmolar hypernatremia. In such patients, it is probably most prudent to confirm the diagnosis with arginine vasopressin.

10. The patient with pheochromocytoma is at significant risk for hypertensive crisis and requires careful blood pressure and heart rate control prior to its surgical removal. Control of hypertension begins prior to surgery and continues after extraction.

11. Hormones of metabolic control such as growth hormone, ghrelin, and leptin, hold special interest during the later phases of critical illness, when failure to reestablish appropriate levels and pulsatility may contribute to delayed recovery and rehabilitation. Correctional interventions at this stage may potentially curtail post-ICU syndrome and aid rehabilitation.

GENERAL IMPACT OF CRITICAL ILLNESS ON ENDOCRINE AND METABOLIC HOMEOSTASIS
The brain maintains its systemic control over peripheral organ systems via direct neuronal connections (e.g., autonomic) and by circulating substances that are centrally sensed and released. Severe illness disrupts responses among the various hormonal axes that during health are well coordinated and guided by diurnal circadian rhythms.

Signaling cross talk between circulating inflammatory cytokines and the neurohormonal axis has been well demonstrated for severe sepsis. During such life-threatening illness, baseline levels of key hormones as well as normal diurnal patterns of pulsatile release and suppression are impressively affected, with both positive and adverse consequences (Fig. 32-1). Simultaneously, hormonal clearance may be impaired by organ dysfunction. The hypothalamic-pituitary-adrenal (HPA) axis provides one salient example, as expressed by exaggerated concentrations of cortisol. The benefits of this initial response, however, become less convincing as the elevated cortisol levels persist through the subacute/chronic and recovery phases (Fig. 32-2). Whereas the body's initial responses to illness of moderate severity seem geared toward restoring effective homeostasis, the challenge often proves overwhelming, and initial reactions may turn counterproductive as time goes on. Persistence of such responses into the later stages—aided in large part by impeded hormonal processing and breakdown—may delay effective recovery. At the mitochondrial level, energy production may be compromised by inflammatory cytokines or perhaps adaptively shut down in response to inadequate perfusion. Such disturbances, in conjunction with the aggressive steps we take to address pathobiology, assure comfort, and maintain vital signs, cause departures from normal endocrine regulation, coordination, and diurnal rhythms. The resulting dysfunction suggests that metabolic supports and hormonal interventions should be timed and modified according to illness stage and metabolic need (see Chapters 16 and 27).

**FIGURE 32-1.** As exemplified by growth hormone (GH), critical illness alters the amplitude and pulsatility of neuroendocrine hormones. The pattern changes with stage of illness and recovery.
FIGURE 32-2. Schematic depiction of time course of serum cortisol, the endocrine organ stimulating hormones of the anterior pituitary gland, and the response to them of the targeted organs.

Because of breakdown of lipids, exuberant cortisol release, gluconeogenesis, and inhibition of growth hormone’s normal stimulation of the liver-generated insulin-like growth factors (ILGFs), severe inflammation is often accompanied by an initial surfeit of energy sources coupled with accelerated breakdown of muscle protein. This combination mandates that restraint of calorie administration is prudent during the early rescue stage, that efforts to provide additional energy sources parenterally may be unwarranted in those with adequate reserves preadmission to the ICU, and that inhibition of protein catabolism is a logical (if unproven) therapeutic target during this phase (Fig. 32-3). In the subacute, chronic, recovery, and rehabilitation stages that follow rescue, the native hormonal environment as well as metabolic needs and capacities to respond change considerably, dictating that adequate and personalized calorie, protein, and supplemental nutrients be provided, along with minimized sedation and encouragement of mobilization. Synthetic hypothalamic releasing factors for hormones shown deficient during this postacute phase may hold promise to enhance recovery and rehabilitation with relative safety. Higher than normal protein intake, perhaps aided by anabolic hormones, has a defensible rationale for rebuilding depleted protein reserves during the recovery and rehabilitation phases, but this intervention holds a tenuous place in ICU illnesses. Discouraging experience with corticosteroid supplementation and with unregulated and ill-timed dosing of growth hormone underlines that we must select patients wisely and both dose and time endocrine interventions carefully according to tissue requirements and circulating hormone levels. In short, their indications currently remain controversial and tentative. If such interventions do eventually prove of value, awareness of illness stage will certainly be an important consideration.
THYROID DISEASE

Critical Illness, Thyroid Kinetics, and Testing

Thyroid hormone helps mediate cell growth, differentiation, and metabolism. Normally, T4 is converted by peripheral tissues into T3, in both its active form and an altered and inactivated form, reverse T3 (rT3). Rising levels of both T3 and T4 inhibit thyroid-releasing hormone (TRH) from the hypothalamus and thyroid-stimulating hormone (TSH) from the pituitary. The induction of critical illness accelerates conversion of T3 into rT3. The reduced amplitude of the T3/rT3 ratio mimics the adaptive change seen in starvation and is thought to serve initially as a helpful protective response, downregulating cellular energy consumption, and protein catabolism during the acute phase. Depression of the T3/rT3 ratio has been interpreted to correlate with severity of illness and with adverse outcome. TSH levels may transiently bump upward but characteristically drift into the low normal or subnormal range.

Although mild hyperthyroidism and hypothyroidism occur very commonly among the ambulatory population, severe thyroidal dysfunction disease rarely afflicts intensive care unit (ICU) patients. Nevertheless, profound excess or deficiency of thyroid hormone is life threatening, can be confused with many other nonendocrine conditions, and is generally amenable to simple therapy. By far the most common “thyroid disorders” seen in the ICU are not thyroid problems at all but rather laboratory anomalies resulting from altered binding and metabolism of thyroid hormone in the periphery caused by response to critical illness or drug therapy, as described above. Critical illness often affects thyroid tests, in some cases simulating disease when none is present and in other cases obfuscating a true diagnosis. For example, almost all critical illnesses decrease TSH and the plasma concentration of proteins that bind thyroid hormone (albumin, thyroxin-binding globulin). As binding proteins decrease, total levels of thyroxin (T4) and to a lesser degree triiodothyronine (T3) decline, simulating hypothyroidism. In fact more than 50% of critically ill patients have subnormal T4 and T3 levels. Historically, the
term “euthyroid sick” was used to describe the constellation of low T4, T3, and TSH, but a more frequently used contemporary term is “nonthyroidal illness,” or NTI. It now appears that a restricted number of these patients actually do have transient central hypothyroidism. The most common laboratory finding in the NTI (euthyroid sick) patient is a depressed free T3 level. When T4 or T3 is administered to critically ill patients with these laboratory findings, clinical outcomes are seldom improved. Critical illness-induced reductions in plasma protein concentrations can also obscure a true diagnosis of hyperthyroidism by lowering observed T4 and T3 levels into the normal or nearnormal range. (Most patients with true hyperthyroidism have increased T3, even if T4 levels are normal.)

Drugs commonly used in the ICU also complicate thyroid function test interpretation by inhibiting TSH secretion, T4 binding to serum proteins, or T4 to T3 conversion. For example, glucocorticoids, octreotide, dobutamine, dopamine, and dopamine agonists inhibit TSH secretion, potentially leading to an erroneous diagnosis of central hypothyroidism if T4 values are low or to an erroneous diagnosis of hyperthyroidism if T4 is modestly elevated. Highly protein-bound drugs like phenytoin, carbamazepine, furosemide, aspirin, and some nonsteroidal anti-inflammatory drugs displace T4 from binding proteins, lowering total T4 levels, and potentially leading to a false diagnosis of hypothyroidism. Finally, glucocorticoids, amiodarone, and β-blockers all inhibit the peripheral conversion of T4 to T3, resulting in a low serum T3 concentration and encouraging a misdiagnosis of hypothyroidism.

Given the many influences of critical illness on thyroid function tests, several guiding principles should be kept in mind: (1) Do not send “screening” thyroid function studies; tests should be thoughtfully selected to confirm or exclude a specific condition suspected on clinical grounds. (2) Unlike ambulatory practice, where clinical examination and TSH measurement usually suffice to diagnose both hypothyroidism and hyperthyroidism, use of TSH alone in the ICU for diagnosis is fraught with problems. (3) Be suspect of thyroid disease diagnoses made first in critically ill patients.

Severe Hyperthyroidism and Thyroid Storm

No absolute signs differentiate “thyroid storm” from severe hyperthyroidism, although diagnostic criteria have been proposed. Apart from accentuated signs and symptoms of hyperthyroidism, thyroid storm is more likely to exhibit fever (often approaching 103°F) and tachycardia (pulse >100/min). Secondary features may include goiter, proptosis, congestive heart failure, arrhythmias, tremor, diaphoresis, diarrhea, elevated liver function tests, and mental status changes.

Historically, surgery performed on large goiters with poor preoperative preparation was the most common cause of thyroid storm, but currently, this condition most often results from an acute infection, withdrawal of antithyroid drugs, trauma, or non thyroid surgery. Recognizable Graves disease is present in most patients with severe hyperthyroidism. (Toxic multinodular goiter and autonomous thyroid nodules are also fairly common causes.) Although iodine ingestion initially increases T4 production, it suppresses T4 release. However, serum iodine levels decline after 10 to 14 days, allowing discharge of large amounts of newly formed T4 into the circulation. For this reason, intravenous and oral iodinated radiographic contrast studies may precipitate delayed thyroid storm in predisposed individuals. Accidental or intentional overdose with exogenous T3 or T4 is only problematic following massive ingestions.

In the critically ill patient with suspected thyroid storm, the diagnosis must initially be a clinical one. The results of thyroid function tests are often delayed, and comparable elevations in total T4, free T4, and T3 may occur in both mild and severe hyperthyroidism (Table 32-1). When normal or only modestly elevated T4 or T3 levels are detected in patients with clinically overt hyperthyroidism, the finding is usually because of reductions in binding protein levels induced by critical illnesses. TSH is undetectable (<0.01 mU/L) in essentially all cases of true
hyperthyroidism, whereas low but detectable levels of TSH (0.01 to 0.1 mU/L) associated with normal or modestly elevated T3 and T4 levels are usually the result of critical illness alone. T3 thyrotoxicosis is sometimes seen in which plasma free T4 levels are normal and only the T3 concentration is elevated. In general, thyroid hormone levels tend to be higher in patients with storm compared with those having less severe thyrotoxicosis. However, no specific threshold values of plasma T4 or T3 differentiate thyroid storm from thyrotoxicosis.

| Table 32-1. Laboratory Analysis of Thyroid Function |
|---------------------------------|---------|--------|--------|------------------|
|                                 | Free T4 | T3     | TSH    | Notes                                    |
| Primary hyperthyroidism         |         |        |        |                                              |
| T3 toxicosis                    | Normal$^a$ | Elevated$^a$ | Undetectable to low | Graves disease likely, consider T3 poisoning |
| T4 toxicosis                    | Elevated$^a$ | Normal$^a$ | Undetectable to low | Suggests hyperthyroidism with concomitant critical illness or T4 poisoning |
| Central hyperthyroidism         | Elevated | Elevated | Elevated | Very rare. Pituitary tumor likely cause   |
| Critical illness                | Low to normal | Low | Low to normal |                                             |
| Hyperthyroidism plus critical illness | Elevated | Normal | Low |                                             |

Hypothyroidism

|                                 |         |        |         |                                             |
| Primary                        | Low     | Low    | Elevated |                                             |
| Secondary                      | Low     | Low    | Undetectable to low |                                             |

$^a$T4 and T3 can be normal in critical illness.

Elevated hepatic transaminases indicate lifethreatening disease. Rarely, hypercalcemia may be present. In thyroid storm, the leukocyte count is usually normal or slightly elevated, but relative lymphocytosis is common, a feature that may help to differentiate thyroid disease from infectious causes of fever.

Initial pharmacologic treatment of thyroid storm includes multiple components (Fig. 32-4). First, a thionamide agent is given to inhibit thyroid hormone synthesis. Time-honored agents of this type are propylthiouracil (PTU) and methimazole. Propylthiouracil may be given as 1,000 mg orally followed by 200 mg every 4 hours to 400 mg every 6 hours. This drug is a particularly attractive choice in the pregnant patient. Methimazole is a valuable
option and is frequently the first choice drug because hepatotoxicity is sometimes caused by propylthiouracil. Because the thyroid gland serves as a repository of previously synthesized hormone, hormone release may continue for days after synthesis has been stopped. Exogenously administered iodine or iodine-containing compounds control hormone release and should be given routinely after thionamide initiation in patients with thyroid storm (Fig. 32-5). If iodine is given prior to a thionamide agent, thyroid hormone synthesis may be stimulated. A beta-blocker is used to blunt end-organ effects. Propranolol, metoprolol, and esmolol have been used. Closely monitored initial administration of metoprolol 5 to 15 mg intravenously in incremental doses followed by 5 to 15 mg intravenously every 4 to 6 hours a reasonable strategy. Propranolol 40 to 60 mg orally every 6 hours is another option. Finally, an agent to inhibit peripheral conversion of T4 to T3 is given. Dexamethasone 2 mg IV every 6 hours is the most common choice for this purpose.

**FIGURE 32-4. Elements of treatment for thyrotoxic crisis (“thyrotoxic storm”).**
Critical care management of thyroid storm includes acetaminophen and external cooling measures to manage hyperthermia. Aspirin is preferably avoided as an antipyretic, as it may worsen thyrotoxicosis by displacing thyroxine from circulating thyroxine-binding globulin. Giving aspirin may be prudent, however, if an acute coronary syndrome is simultaneously of concern. Other supportive measures include management of cardiac dysrhythmias, tachyarrhythmias, heart failure, and respiratory failure. Routine hydrocortisone coverage (100 to 300 mg/d in divided doses) has been recommended for patients with thyroid storm because of the risk of coincident adrenal insufficiency. Cosyntropin stimulation testing may be performed to exclude that possibility.

As noted above, release of preformed T4 into the circulation is rapidly blocked by ingestion of concentrated iodine (five drops [250 mg] of supersaturated potassium iodide [SSKI] solution q6h). Unfortunately, even complete blockade of T4 release does not terminate hyperthyroid crisis because circulating T4 has a very long half-life and conversion to T3 continues. Peripheral conversion can be inhibited by corticosteroids or propranolol. Because PTU and iodine are only available as enteral preparations, administration may prove difficult in the critically ill. Because iodine inhibits thyroid uptake of PTU and methimazole, these drugs must be administered at least 2 hours before iodine therapy.

β-Blockers blunt important tissue actions of thyroid hormone (especially in the heart) but must be used with caution, particularly in patients with congestive heart failure or bronchospasm. If a β-blocker is used, it makes some sense to initially select a short-acting agent to gauge the patient’s response. If adverse consequences develop, the effects can be rapidly terminated. In deliberate ingestions of excess thyroid hormone, oral administration of bile acid sequestering drugs helps prevent absorption of residual luminal medication. In severe
overdoses, plasmapheresis or peritoneal dialysis may be used to remove thyroid hormone from the circulation.

Heart failure occurs in many patients with thyroid storm. Although classically described as a “highoutput” state, many patients have normal or even low cardiac outputs and elevated ventricular filling pressures; these may be harmed by the use of β-blockers. By contrast, hypertension and tachycardia seen in thyroid storm respond well to selective β-blockade. Associated tachyarrhythmias may be controlled with a combination of β-blockers and calcium channel blockers. Therapy should also include nutritional support because of heightened caloric requirements. (Folate and B vitamins are rapidly consumed and should be supplemented.) Increased thyroid activity accelerates the metabolism of many drugs, including some of those useful in its treatment (β-blockers and dexamethasone); thus, larger doses and/or a more frequent dosing may be necessary.

**Severe Hypothyroidism (Myxedema Coma)**

Hypothyroidism is very common, but its most severe manifestation, “myxedema coma,” is quite rare. Hypothermia, central nervous system (CNS) dysfunction, bradycardia, and hypotension differentiate myxedema coma from simple hypothyroidism. Advanced hypothyroidism contributes to several common syndromes in the ICU including (1) severe ileus suggestive of bowel obstruction, (2) respiratory failure (including failure to wean from a ventilator), (3) heart failure, (4) hypothermia, and (5) coma. Myxedema sufficient to induce coma is a serious and potentially fatal disorder.

In more than 90% of cases, hypothyroidism results from primary failure of the thyroid gland, not pituitary insufficiency. Making a *de novo* diagnosis of myxedema in the ICU is uncommon. Most patients hospitalized with severe hypothyroidism have carried the diagnosis for some time; their admission is usually precipitated by the combination of discontinued thyroid replacement therapy and/or intercurrent illness (e.g., infection, myocardial infarction, surgery, hypothermia, trauma, and drugs, particularly sedatives). For unclear reasons, hypothyroidism is much more likely to occur in older patients, in women, and in the patient with long-standing disease.

Precursor symptoms of myxedema coma are consistent with overt hypothyroidism. Fatigue, weakness, myalgias, mental status changes, constipation, cold intolerance, and daytime somnolence are typical. Physical findings include hypothermia, lethargy, dry and coarse skin, brittle hair, macroglossia, hoarseness, and goiter. There may be bradycardia and conduction disturbances with distant heart sounds and signs of pleural or pericardial effusion. Deep tendon reflexes may be hypoactive with a delayed relaxation phase or entirely absent. To qualify as having myxedema coma, there must be some alteration in sensorium ranging from confusion to obtundation.

Associated features, such as normocytic anemia, hyponatremia, hypoglycemia, hypercapnia, and hypoxemia, are frequent but nonspecific. When hypoglycemia is noted, concurrent adrenal insufficiency is possible. Marked elevations of cholesterol are frequently noted, and above normal levels of creatine phosphokinase are typical. The hyponatremia encountered in hypothyroidism is often multifactorial, reflecting inappropriate antidiuretic hormone (ADH) secretion and combined treatment with diuretics and hypotonic fluids.

Frequent laboratory findings of hypothyroidism include hyponatremia, hypoglycemia, hyperlipidemia, and increased plasma creatine phosphokinase activity. Blood gas analysis may reveal hypercarbia and impaired oxygenation. Respiratory responses to hypercapnia and hypoxemia are blunted, and respiratory failure often complicates myxedema coma. In general, TSH is increased, sometimes to high levels. Free T4 concentration in plasma is below normal.

Abnormalities in plasma thyroid hormone levels often characterize critically ill patients with no clinical evidence of thyroid disease. This is the “sick euthyroid/NTI” already discussed above and does not require hormone administration. The most common laboratory abnormality in sick euthyroid syndrome is a depressed level of free T3. This finding persists throughout acute illness. Free T4 tends to remain
normal or may briefly rise to supranormal levels. However, in most severe forms of critical illness, the free T4 level may fall into the subnormal range. Thyrotropin is least affected by nonthyroidal illness but may decrease in severely ill patients. An inactive isomer of T3 known as reverse T3 is elevated in the sick euthyroid syndrome.

The treatment of severely symptomatic hypothyroidism (myxedema coma) is directed at hormone replacement, associated electrolyte disturbances, and supportive care of the respiratory system (Fig. 32-6). Because orally administered drugs are absorbed poorly in myxedema, medications should initially be administered intravenously (IV). Initial medication management of myxedema coma is IV administration of levothyroxine. A loading dose of 300 to 700 μg IV is given followed by daily maintenance doses of 100 μg intravenously, later replaced by 50 to 200 μg orally. An optional adjunct to levothyroxine therapy is liothyronine, which is given as an initial dose of 10 to 25 mg IV followed by 10 mg IV every 8 hours until the patient stabilizes. Finally, support for adrenal insufficiency is given with hydrocortisone 100 mg IV every 8 hours. Clinical improvement usually begins within 12 to 24 hours. When hypothyroidism is suspected, adrenal function must also be tested because a hemodynamic crisis may be precipitated if T4 is administered to patients with concurrent adrenal insufficiency. To avoid missing the diagnosis, the most practical approach is to perform an adrenocorticotropic hormone (ACTH) stimulation test when thyroid function tests are obtained, and begin empiric stress doses of glucocorticoids (hydrocortisone 100 mg IV q8h) while awaiting the results (see Classic Adrenal Insufficiency, following). If baseline cortisol levels exceed 25 μg/dL, hydrocortisone can be discontinued. Hypoglycemia occurs frequently enough to warrant urgent evaluation in acutely ill patients with altered mental status and suspected hypothyroidism. Arterial blood gases (ABGs) should be analyzed in most patients because suppressed ventilatory drive leading to hypercapnic respiratory failure occurs commonly. Hyponatremia is effectively treated by temporary water restriction. Hypotension and hypoperfusion should be treated with T4 and corticosteroids as well as fluids and vasopressors, as dictated by usual hemodynamic parameters. Many patients will have concomitant hypothermia that is best treated with passive external rewarming (see Chapter 28).
FIGURE 32-6. Elements of treatment for severe hypothyroid crisis.

Aspiration pneumonitis (often leading to acute lung injury) is a noted complication in patients with reduced mental status secondary to hypothyroidism.

The obesity and immobility of the profoundly hypothyroid patient predispose to the formation of atelectasis, decubitus ulcers, and deep venous thrombosis. Hypothyroidism often produces disorders of sleep and breathing, which are usually clinically overt.

ADRENAL DISEASES

Classic Adrenal Insufficiency

The physiologic effects of adrenal insufficiency result from deficiencies of cortisol and/or aldosterone (Table 32-2). Loss of mineralocorticoid action is responsible for most of the significant manifestations seen in the ICU. Regardless of whether the disease results from adrenal (primary) or pituitary gland (secondary) failure, most symptoms are mild and well compensated until a second process causes volume depletion (vomiting, diarrhea).
or vasodilation (sepsis, drugs, surgery). Until the supervening illness occurs, loss of aldosterone is compensated for by increased salt and water intake.

The most common and severe form of the disease, primary adrenal insufficiency, results from direct adrenal gland destruction. Tuberculosis, fungal disease, surgery, infarction, metastatic cancer, autoimmune disease, and hemorrhage are the most frequent causes. Hemorrhagic adrenal insufficiency, though quite uncommon, is occasionally encountered in septic or in anticoagulated patients, especially after cardiopulmonary bypass. Critically ill patients with acquired immunodeficiency also have a high frequency of adrenal insufficiency. In patients with AIDS, cytomegalovirus, metastatic neoplasm, and ketoconazole therapy are common culprits; yet in many patients, the etiology remains obscure. In primary adrenal insufficiency, pituitary secretion of ACTH increases in an attempt to stimulate the dysfunctional adrenal glands to maintain normal cortisol levels. Because both mineralocorticoid (aldosterone) and glucocorticoid functions are lost, clinical manifestations are more severe and in important respects differ from the secondary form of the syndrome.

### Table 32-2. Cortisol and ACTH Levels in Adrenal Diseases

<table>
<thead>
<tr>
<th>Pituitary Adrenal Axis Status</th>
<th>ACTH Level</th>
<th>Baseline</th>
<th>Post-ACTH Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Primary adrenal failure</td>
<td>Marked increase</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Secondary adrenal failure</td>
<td>Low or normal</td>
<td>Low</td>
<td>Increased</td>
</tr>
<tr>
<td>Poststeroid withdrawal</td>
<td>Low</td>
<td>Low or normal</td>
<td>Mild increase(^a)</td>
</tr>
</tbody>
</table>

\(^a\)Requires 24-hour ACTH infusion for confirmation.

Secondary adrenal insufficiency because of pituitary gland insufficiency results from head trauma, tumor (especially adenoma), or infarction. Infarction may occur when hemorrhage occurs into a preexisting pituitary adenoma, when primary hemorrhage occurs in the anticoagulated patient, when trauma disrupts a feeding artery, or when the postpartum patient suffers spontaneous infarction. Secondary adrenal insufficiency results in lower cortisol, but aldosterone secretion remains normal because it is not regulated by ACTH, and the adrenal gland itself is unaffected. However, because cortisol is required for normal synthesis of catecholamines, blood pressure can decline modestly from glucocorticoid deficiency alone. The abrupt withdrawal of chronically administered exogenous steroid mimics secondary adrenal insufficiency, as ACTH secretion is suppressed, and the exogenous corticosteroid is rapidly cleared from the circulation. Because aldosterone levels remain near normal, secondary adrenal insufficiency seldom results in the dehydration or hyperkalemia prominent with the primary form of the disease. During the stress of critical illness from any cause, cortisol breakdown may initially be impaired, signaling the hypothalamic-pituitary link to halt stimulation of the adrenal gland. Over the ensuing days to weeks, cortical atrophy may be initiated, resulting in a form of secondary adrenal insufficiency that contributes to the symptoms and vulnerabilities of chronic critical illness. In such cases, judicious corticosteroid replacement is indicated, and encouraging ACTH release may offer a logical therapeutic approach.
A rare, tertiary form of adrenal insufficiency also exists in which granulomatous disease (e.g., sarcoid) or neoplasm destroys the hypothalamic pathways necessary for signaling the pituitary release of ACTH. Diagnosis and treatment parallel that of secondary adrenal insufficiency.

The drugs, ketoconazole, etomidate, and aminoglutethimide all interfere with normal steroidogenesis, and under specific circumstances, they have the potential to precipitate adrenal insufficiency. Other drugs that accelerate hepatic metabolism of exogenously administered corticosteroids (e.g., rifampin, phenytoin, and barbiturates) can also precipitate adrenal insufficiency. Observational studies associating etomidate use with worse clinical outcomes in critically ill patients have prompted substantial controversy. Undoubtedly, etomidate suppresses cortisol release for 12 to 24 hours, but a cause-and-effect relationship to morbidity or mortality is highly suspect. Because etomidate is often the sedative chosen for intubation for the sickest patients, it is not surprising that they might have worse outcomes for reasons unassociated with the adrenal hormones. The causality argument is further challenged by the observation that administration of hydrocortisone and etomidate together does not result in better outcomes than using etomidate alone.

Signs and symptoms of adrenal insufficiency are nonspecific. A constellation of findings may suggest the diagnosis. Among symptoms arising from lack of adrenocortical hormones are anorexia, nausea, emesis, abdominal pain, diarrhea, weight loss, fatigue, weakness, orthostasis, myalgias, amenorrhea, and salt craving. Physical findings include low-grade fever, tachycardia, orthostasis, abdominal tenderness, confusion, and galactorrhea. A provocative factor such as intercurrent illness or surgery often triggers a crisis. Volume depletion is prominent in primary adrenal failure but less likely in secondary causes because mineralocorticoid elaboration is regulated by the renin-angiotensin system, rather than by corticotropin.

Regardless of cause, hyponatremia is a nearly universal (approx. 90%) finding. Urinary Na⁺ wasting resulting in hyponatremia and renal K⁺ retention are seen predominately in primary adrenal insufficiency because of the loss of aldosterone. Conversely, isolated cortisol deficiency from secondary adrenal insufficiency impairs free water excretion but less commonly causes hyperkalemia. The mechanism of impaired free water clearance is unknown but may partly result from increased ADH secretion occurring in an attempt to offset hypovolemia. Hypercalcemia, though unusual, may be seen in either form of adrenal insufficiency because cortisol limits gastrointestinal absorption of calcium and increases its renal excretion. Although the total leukocyte count is usually normal, the percentages of eosinophils and lymphocytes are often increased. Mild normochromic normocytic anemia is very common. Hypoglycemia may be the presenting manifestation of either primary or secondary adrenal insufficiency but is much more common in children than adults. (Cortisol boosts glucose levels by increasing gluconeogenesis and catecholamine levels.) The volume depletion seen with all forms of adrenal insufficiency results in elevations of the blood urea nitrogen (BUN).

Confirmation of adrenal insufficiency may be accomplished using the quick cosyntropin stimulation test. After a baseline blood specimen is obtained for plasma cortisol, 250 μg of cosyntropin is then given intravenously. Blood specimens at 30 and 60 minutes after cosyntropin administration are collected for cortisol assays. Adrenal failure is likely present if a prestimulation cortisol level is less than 3 μg/dL or the highest poststimulation cortisol level is less than 18 μg/dL. Random levels greater than 18 μg/dL probably exclude most causes of adrenal insufficiency in patients who are not severely ill, but higher levels may represent an inadequate response in patients who are profoundly stressed. The so-called relative adrenal insufficiency of sepsis has been defined as a peak increase in plasma cortisol of 9 μg/dL or less following cosyntropin stimulation in the setting of septic shock. To put this into perspective, it is helpful to note that the random cortisol level of a seriously ill patient is 30 to 50 μg/dL. (Cosyntropin testing is generally not employed in the setting of sepsis or septic shock.) Routine treatment of this variant consists of hormone replacement, intravascular volume expansion, and dextrose administration.
Hydrocortisone administration prior to stimulation testing will invalidate test results due to cross-reactivity of the cortisol assay with hydrocortisone. To avoid delaying therapy in the setting of shock, a single dose of dexamethasone may be given prior to cosyntropin testing because dexamethasone does not cross-react with the cortisol assay. Hydrocortisone is substituted as soon as the final cortisol assay specimen is obtained. Current recommendations for treating relative adrenal insufficiency associated with septic shock call for limiting therapy to patients with shock refractory to intravascular volume expansion and catecholamine vasopressor infusion (Table 32-3). Treatment may be initiated with a loading dose of 100 mg followed by either 50 mg of hydrocortisone intravenously every 6 hours or a continuous intravenous infusion of hydrocortisone at 8.3 mg/h.

<table>
<thead>
<tr>
<th>Table 32-3. Stress Replacement Doses of Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Hydrocortisone</td>
</tr>
<tr>
<td>Methylprednisolone</td>
</tr>
<tr>
<td>Prednisone</td>
</tr>
</tbody>
</table>

Therapy for acutely overt adrenal insufficiency has four components. Hydrocortisone is given beginning with 200 mg IV followed by 100 mg IV every 8 hours or 12.5 mg/h by continuous IV infusion. Hydrocortisone dosing is reduced to 50 mg IV every 6 hours over several days and ultimately tapered to physiologic replacement after acute illness subsides. Fludrocortisone at 50 to 200 μg orally daily may be considered if hydrocortisone doses are less than or equal to 100 mg/d. Volume repletion using normal saline or balanced salt solution is fundamental to effective treatment and is often accomplished by giving 2 to 3 L of fluid initially. Fluid infusion is then titrated to ensure adequate intravascular volume. Finally, a maintenance infusion of 5% dextrose in normal saline is provided to maintain normal blood glucose concentration. Blood sugar should be checked frequently to guide titration of dextrose administration. Table 32-4 provides equivalent doses of corticosteroids for replacement therapy.

<table>
<thead>
<tr>
<th>Table 32-4. Relative Potency of Available Steroid Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
</tr>
<tr>
<td>Betamethasone</td>
</tr>
<tr>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Hydrocortisone</td>
</tr>
</tbody>
</table>
Withdrawal of Exogenous Steroids

A Cushingoid appearance should always be a clue to the use of exogenous corticosteroids and the potential for pituitary-adrenal axis suppression. Symptomatic adrenal insufficiency as a result of withdrawing exogenous steroid therapy is a surprisingly rare event, considering the frequency with which corticosteroids are used. The likelihood of developing adrenal insufficiency following withdrawal of steroids relates directly to the prior daily dose of corticosteroid and the duration of therapy. Partial or complete adrenal suppression from exogenous corticosteroids may occur with as little as 7 days of low-dose prednisone (20 to 30 mg). Prolonged steroid use may impair adrenal responsiveness for as long as 1 year after withdrawal of exogenous steroids (Fig. 32-7). After discontinuing exogenous corticosteroids, the ACTH response returns first (usually within 90 days); however, several months often pass before normal cortisol responsiveness to ACTH is restored. Patients who demonstrate a normal response to ACTH stimulation are unlikely to mount an inadequate adrenal response to stress. If the adrenal responsiveness of a critically ill patient is questionable, adrenal function should be tested and cortisol replacement empirically given. In patients of questionable adrenal status who require immediate surgery, administration of 100 mg of IV hydrocortisone before and after surgery will provide sufficient perioperative coverage.

Methylprednisolone 4 5 0 18-36
Prednisolone 4 5 1 18-36
Prednisone 5 4 1 18-36
Fludrocortisone a 10 125 18-36

*aThis agent is not used for glucocorticoid effects.*
FIGURE 32-7. ACTH and cortisol levels following abrupt termination of prolonged glucocorticoid therapy. ACTH, adrenocorticotropic hormone.

**Excessive Corticosteroid Administration**

High doses of corticosteroids predispose to infection, protein wasting, poor wound healing, mental status alterations, and glucose intolerance. Exposure to as little as 1 to 2 weeks of high-dose corticosteroid has been associated with significant neuromyopathy. Long-term exposure may also cause intracranial hypertension, bone loss, aseptic necrosis, glaucoma, pancreatitis, and cataract formation. Adverse steroid effects are minimized by: (1) using the lowest effective dose, (2) using a shorter-acting steroid preparation such as hydrocortisone, (3) administering the full daily requirement in a single morning dose, and (4) using alternate day therapy.

**DISORDERS OF GLUCOSE METABOLISM**

**ICU Glucose Control**

Glucose abnormalities occur commonly in the ICU for several reasons: (1) Critical illness induces a state of relative insulin resistance owing to release of stress hormones (glucagon, epinephrine, growth hormone, and cortisol) as well as relative insulin insensitivity. (2) Inconsistent feeding unpredictably alters the glucose load. (3) Sepsis, renal insufficiency, and drug therapy (catecholamines, octreotide, corticosteroids) change the normal effectiveness of glycemic control.

Over recent years, the topic of glucose management has been one of the most tumultuous areas in critical care. There seems to be incontrovertible evidence that hyperglycemia itself (rather than insulin lack) is proinflammatory and attended by a variety of adverse consequences. Brain functioning and its recovery from hypoxic or ischemic insults are clearly affected adversely by high levels of glucose. Driven by scientific laboratory observations and well-conducted clinical studies showing that “tight” regulation of blood glucose reduced long-term morbidity of diabetics and postoperative patients, the pendulum in most categories of critical care rapidly swung from allowing “loose” upper limits for blood sugar control to enforcing “strict” normoglycemia. Anti-inflammatory and antithrombotic effects of normoglycemia were hypothesized. Questions regarding the advisability of strict glucose control arose after further studies of a general medical ICU population, where benefit appeared to be restricted to the sickest patients with longer stays. Subsequent clinical trials undermined enthusiasm for stringent glucose control by failing to demonstrate outcome benefits and showing increased risk of hypoglycemia, especially during the earliest phase of critical illness when caloric intake is restricted. The impact of glycemic control may be different in the diabetic and nondiabetic patient. Thus, the optimal blood sugar target may vary for different patient groups. Eagerness to maintain normoglycemia was also dampened by practical issues. Even though insulin is inexpensive, tight glucose control comes at a relatively high price. Sampling site and technique matter, and errors because of detection and timing of insulin administration are a risk unless accurate monitoring is facilitated and infusions regulated by automated bedside equipment. Lacking these supports, hypoglycemia occurs frequently and nursing time required to achieve safe rigorous glycemic control is substantial. Annoyance of intermittent blood sampling to the patient goes without saying.

Given the potentially conflicting data on glucose control in the critically ill patient, what is a reasonable course of action? For most patients,

the following suggestions would seem a sensible approach to managing the critically ill, nonketotic patient: (1) Establish a standardized glucose management protocol and track its performance. Allow serum glucose values to fluctuate within a judiciously liberal range, targeting normal values but erring toward the side of moderate hyperglycemia (<150 to 180 mg/dL) on the upper end. (2) Use enteral feeding when possible and avoid interruptions. (This is best accomplished using a feeding protocol.) (3) Minimize use of long-acting insulin,
especially during the initial phase of ICU care. (Instead, monitor blood glucose values frequently and treat with continuous insulin infusions or smaller intermittent doses of regular insulin.) (4) Avoid oral hypoglycemic agents (i.e., sulfonylureas, meglitinides, biguanides, or thiazolidinediones): their hypoglycemic effects may persist much longer than desired. (5) Use a reliable glucose monitoring system.

Hypoglycemia

Hypoglycemia is a relative term used to describe a blood glucose level insufficient to meet metabolic demands. Defined in this way, hypoglycemia is a rare occurrence among normal patients not receiving insulin or oral hypoglycemic agents because there are numerous endogenous protective mechanisms. These include reactive suppression of insulin secretion and increases in levels of epinephrine glucagon, cortisol, and growth hormone. Although many patients are symptomatic at glucose concentrations less than 50 mg/dL, a large number of young, otherwise healthy patients may have lower glucose levels without symptoms. Although frequently blunted in the critically ill, early symptoms of hypoglycemia are generally those of adrenergic excess (e.g., sweating, anxiety, tremor, tachycardia, and hypertension) and depend not only on the absolute glucose value but also on the rate of its decline. Blood glucose should be rapidly measured in patients with altered mental status to rule out hypoglycemia, even if focal neurological deficits are present. Seizures may also be the presenting symptom but are a more common manifestation in children than in adults. If glucose concentrations cannot be readily measured in a patient with suspected hypoglycemia, administration of 50 to 100 mL of concentrated dextrose with an appropriate amount of thiamine is indicated.

Insulin Reactions

Insulin reactions occur commonly in the ICU because renal insufficiency impairs insulin clearance and hospitalized patients frequently do not receive regular feedings. (Long-acting insulins amplify this risk.) Insulin-induced hypoglycemia may also occur when insulin injected into suboptimally perfused tissue is later absorbed as perfusion improves. Because angiotensin-converting enzyme inhibitors increase an individual’s sensitivity to insulin and enhance glucose uptake, their use has been associated with a higher incidence of hypoglycemia. High insulin levels and low C-peptide levels in a hypoglycemic patient suggest intentional or inadvertent insulin overdosage. The very rare combination of high insulin levels with high C-peptide levels in a hypoglycemic patient is indicative of insulinoma. Patients with little or no functional pancreatic tissue are at particular risk for hypoglycemia because of their inability to produce and release the counterregulatory hormone, glucagon. In addition, drugs that block the adrenergic response (especially β-blocking drugs) can blunt the counterregulatory effects of epinephrine released during a hypoglycemic crisis.

Oral Hypoglycemic Agents

Oral hypoglycemic agents are a poor choice for glucose control in the critically ill because of their duration of action, which is further prolonged by advanced age, renal insufficiency, and frequent interactions with other drugs. Patients with hypoglycemia due to these agents should be observed closely because of the potential for sustained or recurrent symptoms. Hypoglycemia from oral agents is often refractory to glucose alone and may require combined therapy with hydrocortisone and glucagon. Hypoglycemic action of these agents is also potentiated by Butazolidin, sulfonamides, probenecid, and salicylates. Furthermore, oral hypoglycemics interact with such commonly used medications as phenytoin, phenothiazines, rifampin, and thiazides. Metabolic (lactic) acidosis is a side effect of metformin, previously one of the most frequently used oral hypoglycemic agents. Metformin may accentuate the acidosis observed from other causes, but clinically significant acidosis resulting only from doses of this agent given in the therapeutic range is quite uncommon. Risk is increased when the drug is used in patients with renal insufficiency, hepatic insufficiency, or alcohol abuse and among patients with hypoxia or shock. Metformin
should also be stopped for at least 24 to 48 hours in patients undergoing procedures involving radiographic contrast to avoid unusually high drug levels and subsequent lactic acidosis, should renal insufficiency develop.

**Other Causes of Hypoglycemia**

Severe sepsis may produce hypoglycemia by multiple mechanisms including hepatic hypoperfusion, renal insufficiency, depletion of muscle glycogen, and starvation. Alcohol suppresses gluconeogenesis, discourages nutrient intake, and induces a low insulin state that favors free fatty acid release and ketone production. Consequently, alcoholics may present with hypoglycemia and a mixed ketoacidosis/lactic acidosis. By the time such patients seek medical attention, the ingested alcohol has often been completely metabolized, and thus, blood alcohol levels are zero. Glucose, thiamine, and fluids comprise the key elements in the treatment of alcoholic acidosis with hypoglycemia. Although ketoacids are present, insulin does not speed resolution of the acidosis and may precipitate or exacerbate hypoglycemia. Sodium bicarbonate is rarely necessary and possibly should be reserved to address arterial pH less than 7.10. Other causes of hypoglycemia include hepatic failure (because of cirrhosis, tumor infiltration, or fulminant hepatic failure), renal failure, salicylate poisoning, and insulin-secreting tumors. Surgery and other stress states blunt the effect of insulin while stimulating the release of counterregulatory hormones. Imbalance of these effects may cause circulating glucose to unpredictably rise or decline to dangerous levels. To prevent hypoglycemia in the surgical patient, it is prudent to monitor glucose closely and to decrease (but not discontinue) preoperative insulin. A useful strategy is to administer one half of the regular insulin dosage before surgery despite the fasting state. The key to preventing hypoglycemia is frequent intraoperative and postoperative glucose testing.

Artifactual hypoglycemia may occur when glucose is metabolized in blood samples with extremely high leukocyte counts. Leukocyte-associated hypoglycemia is most common when measurement is delayed for hours. Inactivating leukocyte metabolism using oxalate-fluoride containing blood collection tubes can prevent this problem.

**Treatment of Hypoglycemia**

Unless otherwise contraindicated, IV glucose should be empirically administered to all patients with abruptly altered, undiagnosed changes in mental status or neurological function, even when focal. One or two ampules of D50W (100 mg glucose) should be sufficient to acutely raise the serum glucose levels above 100 mg/dL. Larger doses simply increase serum osmolality. When hypoglycemic patients of unknown or questionable nutritional status are treated with glucose, thiamine (1 mg/kg) should be given concurrently to prevent Wernicke encephalopathy. In all cases of hypoglycemia, it is prudent to closely monitor the patient and recheck the serum glucose frequently. On rare occasion, hypoglycemia is refractory to bolus glucose administration alone. In such cases, constant infusion of D10W, with hydrocortisone (100 mg IV) and/or glucagon (1 mg IV per liter of D10W), will augment the blood glucose.

After initial dextrose administration, a maintenance infusion should be started. For the patient with mild to moderate hypoglycemia, 5% dextrose is appropriate. Patients with more severe or refractory hypoglycemia should receive 10% dextrose intravenously. Patients already on 5% dextrose intravenously should increase the intravenous rate or dextrose concentration to 10%. The patient with refractory hypoglycemia despite multiple intravenous dextrose boluses and a 10% dextrose infusion should be considered for hydrocortisone, diazoxide, or continuously infused glucagon or octreotide. Because octreotide suppresses insulin release, it may be useful to treat hyperinsulinemic hypoglycemia.

**Diabetic Ketoacidosis**

Diabetic ketoacidosis (DKA) is a common, serious condition, the mortality of which remains significant despite aggressive therapy. DKA is the result of a deficiency of insulin, usually with a relative excess of
counterregulatory hormones. Most commonly, DKA is precipitated by noncompliance with diet or medication, although infection frequently contributes. Cocaine and corticosteroid use, stroke, myocardial infarction, trauma, pregnancy, pancreatitis, and hyperthyroidism are also potential precipitants.

The most prominent physical features of DKA (hypotension, hypoperfusion, and tachypnea) are the result of the two major metabolic derangements—volume depletion and metabolic acidosis. Volume depletion tends to be less profound in DKA than in hyperosmolar nonketotic syndrome, perhaps because the acidosis of DKA brings patients to medical attention sooner. Deep and rapid “Kussmaul” respirations are an attempt to compensate for metabolic acidosis. Recognition of DKA is not difficult, but some “classic” features are seldom seen. For example, whereas obtundation is frequent, frank coma is rare (<10% of cases). In addition, neurological manifestations are usually less severe than with hyperosmolar nonketotic coma (HNKC). Fever is not a part of DKA in the absence of infection. In fact, slight reductions in temperature are much more frequent. (This is particularly true if the temperature is measured orally in a nonintubated, hyperventilating patient.) Vomiting is quite common, often the result of ileus induced by ketonemia, dehydration, and electrolyte imbalances. Unexplained features of DKA include pleurisy and abdominal pain. The fact that abdominal pain almost always resolves rapidly with correction of the acidosis can help distinguish DKA from more serious causes. Therefore, patients with undiagnosed acute abdominal pain should have glucose and ketone determinations before undergoing other diagnostic or “therapeutic” procedures.

In DKA, metabolic acidosis is often the major finding, whereas the serum glucose concentration generally stays below 800 mg/dL—characteristically, 350 to 500 mg/dL. (However, serum glucose concentrations may be found to be considerably higher in patients with DKA who are comatose.) Ketone measurements should be made initially in patients with hyperglycemia to confirm the diagnosis, but there is little value in serial measurements of ketones or pH. In patients with DKA, three ketones are present in chemical equilibrium: acetoacetate, acetone, and β-hydroxybutyrate, but only acetoacetate and acetone are regularly measured. Normally, β-hydroxybutyrate exceeds acetoacetate by a 3:1 ratio, but in severe acidosis, β-hydroxybutyrate may be present in concentrations 12-fold greater than acetoacetate. As the acidosis improves, the dynamic equilibrium shifts in favor of acetoacetate and ketone concentrations may appear to worsen (another potential reason not to order serial determinations). Note that captopril and other sulfhydryl-containing drugs like penicillamine can react with the nitroprusside reagent resulting in a false positive test for ketoacids. Although it is reasonable to obtain a baseline ABG to evaluate adequacy of ventilation, repeated measurements are not necessary. Clearance of the ketoacids and the metabolic acidosis they cause can be simply tracked by the rise in serum bicarbonate and fall in anion gap.

Though elevated, presenting glucose levels tend to be lower in young, well-hydrated patients whose preserved glomerular filtration facilitates glucose clearance. Leukocytosis (>20,000/mm³) with a predominance of granulocytes may occur even in the absence of infection. Loss of free water because of osmotic diuresis usually leads to hyperosmolarity and hemoconcentration; therefore, even mild reductions of measured packed cell volume in patients with DKA suggest severe underlying anemia or active bleeding.

The osmotic effect of glucose draws water from the intracellular to the extracellular space, producing hyponatremia in most patients. Measured sodium (Na⁺) concentration typically declines approximately 2 mEq/L for each 100 mg/dL increase in glucose. Because glucose seldom exceeds 1,000 mg/dL, it is unlikely for the Na⁺ to fall below 120 mEq/L on an osmotic basis alone. Artifactual depressions of Na⁺ concentration may be seen in DKA when high levels of triglycerides contribute substantially to plasma volume (“pseudohyponatremia”). In patients with profound and prolonged hyperglycemia, especially those with impaired water intake, the resultant osmotic diuresis can result in hypernatremia.
Because acidosis, insulin deficiency, and the osmotically induced flow of water out of cells shift potassium (K+) from the intracellular to the extracellular compartment, most patients with DKA have normal or elevated K+ levels despite sizeable (3 to 5 mEq/kg) total body K+ deficits. With appropriate volume expansion, insulin, and correction of the acidosis, K+ values can plummet. At the very least, even an above-normal admission K+ value should be tracked closely. Total body depletion of magnesium and phosphorus are also extremely common. After urine flow is reestablished, it is appropriate to provide replacement therapy of both elements. The serum of patients with DKA is often grossly lipemic. Some automated laboratory chemistry analyzers misinterpret this turbidity as “hemolysis.” Such reports often prompt repeated testing, until the actual problem is recognized. Direct consultation with the laboratory is indicated when a properly obtained specimen is reported as hemolyzed. Serum creatinine is commonly elevated by dehydration-induced decreases in glomerular filtration rate (GFR). For obscure reasons, the serum amylase is elevated in 15% to 25% of patients with DKA. Hence, finding an increase of amylase less than three times normal does not confirm a diagnosis of pancreatitis. Lipase is less likely to be influenced by DKA and more reliably indicates pancreatic inflammation.

**Management of DKA**

Treatment of DKA prioritizes correction of fluid and electrolyte abnormalities such as hyperosmolality and hypovolemia, as well as correction of potassium and phosphorus deficits and administration of insulin. The first step is infusion of isotonic saline to expand extracellular volume and stabilize cardiovascular status. This step also aids insulin responsiveness by lowering plasma osmolality, reducing vasoconstriction, improving perfusion, and reducing stress hormone levels. The single best indicator of successful therapy is narrowing of the anion gap, a measurement reflecting correction of both lactic acidosis and ketoacidosis. In adults, total body fluid deficits range between 5 and 10 L, with Na+ deficits averaging 300 to 500 mEq. Circulating volume should be replenished rapidly (500 to 1,000 mL/h) with infusions of glucose-free, isotonic crystalloid in patients with evidence of hypoperfusion. Potassium is monitored and repleted. In patients with DKA and hypotension refractory to volume repletion, one should consider (1) bleeding (particularly gastrointestinal or retroperitoneal); (2) septic shock, especially from urinary tract infection (UTI) or pneumonia; (3) adrenal insufficiency; (4) pancreatitis; and (5) myocardial infarction.

After initial resuscitation, the aim should be to complete restoration of the volume deficit within 12 to 24 hours while normalizing electrolytes. Isotonic saline and Ringer solution are reasonable alternatives for fluid replacement after initial resuscitation. If only normal saline is used for fluid replacement, one can expect that a *mild* hyperchloremic nonanion gap acidosis will replace the initial *severe* high-anion gap acidosis. Regardless, adverse consequences from the chloride load are modest, as resuscitated patients rapidly self-correct this electrolyte abnormality. Physical examination, urine output, and frequent electrolyte measurements should guide subsequent fluid and electrolyte choices.

Insulin therapy is started in all patients with moderate to severe DKA who have uncorrected and unaddressed hypokalemia. The only indication for delaying insulin therapy is serum potassium values below 3.3 mEq/L, because insulin will worsen hypokalemia by driving potassium into the cells. Because acidosis tends to boost serum potassium concentrations, patients with initial values below 3.3 mEq/L should receive aggressive fluid and potassium replacement prior to treatment with insulin. An initial regular insulin bolus of 0.1 units/kg followed by an infusion of 0.1 units/kg/h suffice for most patients. The initial goals are to begin reducing the anion gap and to lower plasma glucose by 35 to 70 mg/dL each hour. At the outset, laboratory measurements at 1- to 2-hour intervals should guide the rates of insulin and fluid administration. Failure of glucose to decline significantly within 2 to 3 hours indicates insulin resistance and should prompt doubling the insulin dosage. Insulin infusion should be continued until serum ketones are cleared and the anion gap is normalized, even if supplemental
glucose must be used to prevent hypoglycemia. (Practically, this usually requires 12 to 24 hours by which time the patient is usually ready to eat.) In most cases, it is prudent to switch to a glucose-containing IV fluid when blood glucose values reach 200 mg/dL. Premature termination of insulin infusions is the most common cause of relapsing DKA.

NaHCO$_3$ is rarely necessary in DKA. (An argument can be made that NaHCO$_3$ should only be given if the pH is very low or the patient demonstrates refractory hypotension or respiratory failure.) Even though pH correction can help reduce ventilatory requirements and improve diaphragmatic function in patients with respiratory fatigue or limited ventilatory capacity, there are risks. When a large volume of NaHCO$_3$ is given rapidly to a patient with severe acidosis, a huge quantity of CO$_2$ is generated, which must be cleared by the lung. In patients with limited ventilatory capacity, PaCO$_2$ levels can skyrocket, with particularly adverse consequences for the brain and heart. Because the liver regenerates HCO$_3^-$ from ketones and lactate, patients receiving exogenous base frequently develop a "rebound" alkalosis. The osmolality of a 50-mL ampule of NaHCO$_3$ is nearly fivefold greater than normal saline; thus, aggressive therapy may exacerbate hyperosmolarity. In addition, rapid reversal of acidemia shifts the oxyhemoglobin curve leftward, exacerbates hypokalemia, and may cause paradoxical CNS acidosis.

Spontaneous or iatrogenic arrhythmias induced by acid-base and electrolyte disturbances are a major preventable cause of cardiovascular morbidity in DKA. For example, insulin and NaHCO$_3$ can rapidly drive K$^+$ across the cell membranes, dramatically decreasing serum levels. Therefore, after adequate urine flow is reestablished, KCl should be administered to most DKA patients. Usually, 10 to 20 mEq/h is required to maintain normal levels, but on occasion, up to 60 mEq/h may be necessary. Magnesium and phosphate should also be monitored. Hypophosphatemia may decrease 2,3-diphosphoglyceric acid (2,3-DPG) levels and muscle strength, but phosphate administration has not been shown to specifically improve outcome. Risks of phosphate therapy include acute hypocalcemia and tissue deposition of calcium-phosphate complexes, occasionally inducing acute renal failure. Thus, identify true hypophosphatemia prior to replacement. Hypoglycemia, a common complication of aggressive DKA therapy, may be prevented through vigilant monitoring.

**Hyperosmolar Nonketotic Coma**

The term hyperosmolar nonketotic coma is somewhat of a misnomer in that many patients do not have coma but all have dramatic elevations of glucose despite little or no ketosis. Osmolality is dramatically elevated (often >350 mOsm/L) by profound increases in glucose (often >1,000 mEq/L). Insulin levels in HNKC are sufficient to prevent ketone formation but insufficient to prevent hyperglycemia. Patients with HNKC also generate fewer ketones (hence less acidosis), than patients with DKA because they tend to have lower levels of lipolytic hormones (i.e., growth hormone and cortisol). Glycosuria (a compensatory mechanism limiting hyperglycemia) is tightly linked to GFR; therefore, HNKC is more common in the elderly and in those underlying renal dysfunction. Patients with impaired perception of thirst (e.g., the elderly) and/or deprived of access to water are also predisposed. HNKC is often precipitated by an intercurrent illness that produces volume depletion or promotes hyperglycemia (e.g., sepsis, stroke, diarrhea, vomiting, or corticosteroid or diuretic use). Unlike DKA, where the accumulating ketoacids stimulate ventilation and produce dyspnea, HNKC patients are often minimally symptomatic initially and maintain near-normal acid-base status for long periods of time. It is not until profound volume depletion limits organ function that these patients seek medical attention. The chemical and clinical features of DKA and HNKC are contrasted in Table 32-5.

Laboratory features of HNKC are similar to those of DKA except ketoacidosis is absent or minimal, whereas glucose values are higher—often extremely elevated (>1,000 mg/dL). Plasma osmolality may reach 380
mOsm/kg. Hyperglycemia produces the hyperosmolarity that characterizes this disorder. Marked depletion of total body water (average 9 L) is present in HNKC, largely because of a prolonged osmotic diuresis. Although intravascular volume is usually better preserved in HNKC than in DKA (by high glucose levels), it is at the expense of the intracellular compartment. This effect is responsible for the primary clinical expression of HNKC: life-threatening impairment of neurological function. Coma is reported in 25% to 50% of cases. Because the osmotic effect of glucose is required to maintain intravascular volume, insulin administration before restoring circulating volume with isotonic crystalloid can cause sudden and profound hypotension by producing a rapid shift of glucose and water into cells. Total body deficits of K^+ and PO_4^{3-} may approach those of DKA, although at presentation levels of both ions are usually normally or even modestly elevated.

Correction of HNKC must be cautious, as abrupt reversal of serum hyperosmolarity may produce intracellular water intoxication manifested by dysphoria and seizures. Despite differences in pathophysiology, the initial treatment of HNKC is similar to that of DKA in emphasizing initial restoration of circulating volume with normal saline. (In such patients, this fluid is a relatively hypotonic solution.) Initial fluid replacement using D5W or half-normal saline can precipitate rapid cellular swelling (especially in the brain) as fluid enters the dehydrated, hypertonic cells. In general, complete fluid replacement should be targeted to occur over 24 to 48 hours. Insulin therapy, similar to DKA, should be initiated only after circulating volume has been repleted, as evidenced by stable blood pressure, reduction in heart rate, and adequate urine output. Insulin administration and free water repletion should be guided by serial electrolyte and glucose determinations. In general, insulin infusion may be discontinued when serum ketones disappear and the blood glucose concentration declines below 250 mg/dL. A transition can then be safely made to subcutaneous insulin.

<table>
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<th>Characteristic</th>
<th>Diabetic Ketoacidosis</th>
<th>Hyperosmolar Coma</th>
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<tbody>
<tr>
<td>Insulin levels</td>
<td>Very low</td>
<td>Low</td>
</tr>
<tr>
<td>Lipolytic hormone levels</td>
<td>Very elevated</td>
<td>Mildly elevated</td>
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<tr>
<td>Typical glucose concentration</td>
<td>400-800 mg/dL</td>
<td>≥1,000 mg/dL</td>
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<td>&gt;7.3</td>
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<tr>
<td>Ketones</td>
<td>High</td>
<td>Low or absent</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
</tbody>
</table>

**Table 32-5. Features of DKA and Hyperosmolar Coma**

**DIABETES INSIPIDUS**
Diabetes insipidus (DI) is a life-threatening illness resulting from a failure of the pituitary-hypothalamic axis to release sufficient ADH, or a failure of the kidney to respond to the released hormone. Insufficient ADH action prevents adequate water reabsorption by renal medullary collecting ducts. In the ICU, DI is typically first suspected when a very high, hourly urine output is observed in the setting of a rising serum Na\(^+\) concentration. For most ambulatory patients with DI, the serum Na\(^+\) concentration is maintained close to normal by increasing water intake. Conversely, in the critically ill patient unable to obtain water, significant hypernatremia may occur. When polyuria is seen in patients with serum Na\(^+\) concentrations less than 135, DI is rarely the cause, but rather excessive fluid intake is usually to blame. It is important to remember that high hourly urine outputs (approx. 1 L/h) are not always inappropriate; they may occur after massive volume resuscitation, relief of urinary tract obstruction, and in patients with high urinary solute (e.g., urea, glucose, and mannitol) loads. In both DI and water intoxication, the urine is dilute.

Pituitary or hypothalamic trauma or surgery, anoxic brain injury, and cerebral infarction are the most common causes of “central” DI; however, involvement of the pituitary gland with granulomatous disease or metastatic carcinoma is also possible. The sudden development of DI in a patient with increased intracranial pressure is commonly a signal that brain death has occurred. Transient DI lasting 3 to 7 days may follow closely on the heels of head trauma or pituitary injury. In 25% to 30% of patients, no cause for central DI can be determined. The inability of kidneys to respond to ADH is referred to as “nephrogenic DI.” Hypokalemia, hypocalcemia, chronic pyelonephritis, polycystic kidney disease, sarcoidosis, amyloidosis, sickle cell disease, and chronic use of medications such as loop diuretics, vinblastine, amphotericin B, lithium carbonate, and demeclocycline can all impair renal responsiveness to ADH.

Loss of ADH action results in a dilute urine (osmolality <200 mOsm/L) at a time the plasma is hyperosmolar (>280 mOsm/L). In the conscious patient, clinical features include polyuria and polydipsia; however, if oral intake is inadequate, the clinical presentation may be one of hypovolemia. In the ICU, the diagnosis of DI is most safely confirmed by demonstrating a rise in urine osmolality within 2 hours of administration of 5 units of aqueous vasopressin subcutaneously or 2 to 4 \(\mu g\) of des-amino arginine vasopressin (DDAVP) daily in two divided doses. Increases in urine osmolality of ≥50% suggest central DI, whereas lesser rise suggests nephrogenic DI. In central DI, a head CT or MRI scan may demonstrate pathology in the region of the hypothalamus or pituitary. Adrenal failure accompanies DI in about one third of trauma-induced cases and, therefore, should be sought in accident victims with DI.

In patients with significant polyuria associated with central DI, administration of aqueous vasopressin or desmopressin is necessary to limit urine output and decrease the risk of dehydration. Aqueous vasopressin has a short duration of action allowing close titration but is also a potent vasoconstrictor, which may precipitate splanchnic or myocardial ischemia. Vasopressin may be given intravenously (preferred), subcutaneously, or intramuscularly. Desmopressin is a safer alternative because it is essentially devoid of vasoconstriction associated with vasopressin and is typically dosed as 2 to 4 \(\mu g/d\) given subcutaneously or intravenously in two doses. Desmopressin is also available as an intranasal formulation for chronic use, typically given as 10 to 40 \(\mu g/d\) in two or three divided doses.

Vasopressin and desmopressin are generally of no benefit in nephrogenic DI. Drugs implicated as causing nephrogenic DI should be stopped. Polyuria of nephrogenic DI may be reduced by administration of a thiazide diuretic, which induces mild volume contraction, stimulating sodium and water reabsorption at the proximal renal tubule and reduction of water delivery to the distal nephron.

In patients with high urine output, hypotonic intravenous fluids may be given because the urine in DI may be extremely dilute. Correction of half of the free water deficit should be targeted during the first 24 hours and the
remaining deficit over the next 48 hours. Ongoing fluid losses must also be considered. Overhydration leading to iatrogenic diuresis should be avoided as the normal concentration gradient between the renal cortex and medulla may washout.

**PHEOCHROMOCYTOMA**

Pheochromocytoma is a rare neuroendocrine tumor occurring in less than 0.2% of patients with hypertension. Such neoplasms are often discovered incidentally upon examination of a CT or MRI of the abdomen ordered for unrelated indications. Clinical findings include headache, diaphoresis, flushing, palpitations, and associated hypertension. Other potential findings are anxiety, tachyarrhythmias, extrasystoles, chest pain, dyspnea, nausea, and vomiting. The diagnosis is confirmed with biochemical testing. The conventional approach is to assay catecholamines, epinephrine, and norepinephrine, and their metabolic by-products metanephrine, normetanephrine, and vanillylmandelic acid from a 24-hour urine collection. Plasma metanephrine levels may have the highest sensitivity. However, plasma catecholamine levels may be unrevealing unless performed during an episode of symptoms. Once diagnosed, symptomatic patients with pheochromocytoma should undergo resection following appropriate medical preparation. Agents known to provoke a pheochromocytoma paroxysm, such as glucagon, histamine, and metoclopramide, should be avoided. Resecting a pheochromocytoma is a relatively high-risk surgical procedure and is typically done laparoscopically. Cardiovascular and hemodynamic variables are closely monitored. Perioperative medical therapy is focused on control of hypertension and tachycardia with volume expansion, as necessary. Patients with undiagnosed pheochromocytoma who undergo surgery for other reasons have a higher mortality rate because of lethal hypertensive crisis, malignant arrhythmias, and multiorgan failure. The drug of first choice for acute hypertensive emergencies in patients with pheochromocytoma is phentolamine, which is started at 2 to 5 mg given by intravenous injection and repeated at intervals of 5 minutes or more until blood pressure is controlled. Sodium nitroprusside may also be considered for acute blood pressure management.

Perioperative preparation for pheochromocytoma resection combines alpha- and beta-adrenergic blockade. Alpha-blockade is initiated 10 to 14 days preoperatively to normalize blood pressure and expand contracted blood volume. Selective alpha-1 blockers such as prazosin are utilized in many settings and may be preferred to phenoxybenzamine, another commonly used drug, if long-term pharmacologic treatment is necessary. After adequate alpha-blockade has been achieved, beta-adrenergic blockade is initiated, typically 2 to 3 days preoperatively. The beta-blocker employed should never be started prior to alphablockade because blockade of the vasodilatory peripheral beta-adrenergic receptors with unopposed alpha receptor stimulation may lead to further elevation in blood pressure.

Another treatment option for perioperative blood pressure management is administration of a calcium channel blocker. Nicardipine is most commonly used in this setting with a starting dose of 30 mg twice daily of a sustained release preparation. This medication may be continued as an intravenous infusion in the operating room. Many clinicians consider calcium channel blockers to supplement combined alpha- and beta-blockade, particularly if blood pressure control is inadequate with a calcium channel blocker. Another approach to blood pressure management involves administration of metyrosine, which inhibits catecholamine synthesis.

Complications of surgery for pheochromocytoma occur primarily in the settings of severe hypertension, highly active tumors, or repeat interventions for recurrence. Treatment options for hypertensive crises include intravenous sodium nitroprusside, phentolamine, or nicardipine. Nitroprusside is an ideal vasodilator for intraoperative management of hypertensive episodes because of its rapid onset of action and short duration of effect. Phentolamine is a nonselective alpha-blocker available for bolus administration. A test dose of 1 mg is administered and, if necessary, followed by repeat 5-mg boluses or a continuous infusion. The response to phentolamine is maximal in 2 to 3 minutes after bolus
injection and lasts 10 to 15 minutes. Nicardipine can then be started at an infusion rate of 5 mg/h and titrated for blood pressure control up to 15 mg/h.

Cardiac arrhythmias are often managed with a short-acting β-blocker such as esmolol. Postoperative hypotension can be avoided by adequate fluid replacement and careful management of hypoglycemia by glucose infusion. After tumor removal, catecholamine secretion should fall to normal in approximately 1 week.

ENDOCRINE CONSIDERATIONS DURING RECOVERY

With the rising awareness of the lingering disability associated with the intensive care experience (chronic critical illness and the post-ICU syndrome, PICS), key hormones related to anabolic and catabolic regulation have been receiving increased investigative attention. Investigators have become aware of the radically altered and continually changing endocrine environments, requirements, profiles, and sensitivities associated with critical illness. Simultaneously, the sensitivity of target organs to hormonal stimulation as well as the nutritional needs for exogenous calories and protein also differ with stage of illness. It is now clear that in the immediate phase that follows an acute stress such as sepsis, the body's response is to mobilize energy sources from endogenous reserves, breaking down protein and fat to stoke gluconeogenesis and glycogenolysis (Fig. 32-8). At the same time, most nonessential tissues, e.g., skeletal muscle, down-regulate their energy utilization. In patients normally nourished preillness, endogenous sources can provide 50% to 75% of the needed calories during this phase, making logical the provision of hypocaloric (trophic) feeds. Simultaneously, however, muscles initially break down at a rapid pace, and depleted reserves may not rebuild for long afterward. Providing adequate dietary protein is a logical but difficult goal to accomplish by the enteral route, prompting ongoing efforts to find a safe and effective parenteral approach in this early phase. Initially malnourished patients may not be able to generate adequate energy from their meager reserves, so that a more liberal calorie prescription is advisable. For all patients with severe illness, the recovery and rehabilitation phases are marked by improved ability to process calories and protein, lingering depletion of protein reserves, and high nutritional requirements (Fig. 32-9). Determinations of when the transitions between phases of critical illness occur and of how much nutritional support to provide to the individual may be evaluated by noninvasive tests of metabolic state that are currently in the advanced process of development.
FIGURE 32-8. The body’s early response is to generate energy by producing glucose from glycogen breakdown and by neogenesis from substrates provided by lipolysis and proteolysis. Insulin resistance of most nonvital tissues helps boost the blood glucose level.
FIGURE 32-9. Idealized protein and calorie prescriptions for the various stages of lifethreatening critical illness in a typical ICU patient.

Because of this dynamic picture, administered pharmacologic agents may prove helpful or detrimental to eventual outcome, depending on timing, dose, and duration. Any intervention must be selected and regulated with patient’s stage and underlying metabolic status in mind. Exact approaches to glucose, steroid, and thyroid management are still debated, but there is general agreement on most principles. However, at this time, there remains no strong consensus regarding whether and how to manipulate other key hormonal axes during the recovery and rehabilitation stages to improve outcomes. Nonetheless, the generally acknowledged dysregulation of ghrelin, leptin, anabolic, and growth hormone levels during life-threatening illness potentially affords opportunity for helpful interventions geared toward accelerating improvement.

**Ghrelin**

Ghrelin is a gastric peptide with a range of diverse actions. As its primary actions, ghrelin (the “hunger hormone”) increases appetite, glucose oxidation, lipogenesis, and the secretion of growth hormone (Fig. 32-10). In addition, ghrelin has potent inhibitory effects on the expression of proximal proinflammatory cytokines while conferring antimicrobial actions. Interest in ghrelin for extended critical illness includes its effects on metabolism and sleep. The pituitary-somatotropin axis, and specifically ghrelin signaling, may play a role in regulating the diurnal cycles of sleep and wakefulness. Ghrelin receptors in the brain have been localized to the suprachiasmatic nucleus, a key regulator of circadian rhythm.

**Growth Hormone**

Growth hormone (GH), an endogenous anabolic hormone, is normally secreted in a pulsatile pattern that is a requirement for its peripheral metabolic effects. In health, GH responds to stress, food intake, and circadian rhythms. GH stimulates cell growth and hyperplasia as well as influencing cell metabolism. These influences are effected by direct binding to bone and muscle and more prominently by indirect effects of the liver’s production of somatomedins, such as ILGFs. The upshot of these actions is increased protein synthesis and breakdown of fats.
and glycogen for energy. In the subacute and chronic phases of critical illness, a dramatic reduction in GH pulsatile secretion and reduced levels of IGF-I and IGF-binding protein levels are characteristic (Fig. 32-1). These deficiencies may contribute to hypercatabolism, nitrogen wasting, and an inability to rebuild tissues despite apparent control of the problem that initially triggered the critical illness. Evidence of inadequate GH action (diminished IGF-1 and other markers of inadequate protein synthesis) suggests that the recovering patient might respond with functional improvement following a short course of appropriately dosed GH. It must be emphasized, however, that GH given in the wrong dose or at the wrong time (earliest phase) holds serious potential for adverse outcomes.

**FIGURE 32-10. The primary anabolic and catabolic actions of the counterbalancing hormones of chronic energy balance—leptin and ghrelin.**

**Leptin**
Leptin, a so-called “adipokine,” is manufactured primarily by adipose tissue and structurally resembles the inflammation-promoting IL-6 molecule. In some ways, leptin can be compared to ghrelin, in that like ghrelin, it also works both in the hypothalamus and in a diverse set of peripheral tissues, interacting at the cellular level with other metabolic hormones such as GH. Leptin, however, signals satiety and is proinflammatory—characteristics opposed to those of ghrelin. High leptin levels have been correlated with mortality risk and delayed recovery from critical illness. Were a safe and effective antagonist to leptin available, it might find a role during the later phases of acute illness in promoting protein-calorie intake, speeding rehabilitation and curtailing the course of chronic critical illness.

**Exogenous Anabolic Steroids**
Accelerated protein catabolism during the initial stages of critical illness undoubtedly occurs, but whether this response is pathogenic or adaptive for survival cannot be declared with certainty. At the current time, pharmacologic intervention with agents that slow proteolysis (e.g., eritoran) or with anabolic steroids cannot be recommended during the early phase of severe illness and may (analogously to the GH experience) even be counterproductive. However, once recovery has begun and restoration of depleted muscle mass and strength become priorities, dysregulated endogenous control systems may not be up to the challenge, resulting in protracted disability and restrained progress in rehabilitation. During this stage, judicious and monitored use of
anabolics such as nandrolone and oxandrolone, given in conjunction with appropriately constituted feedings and a program of mobilization and strength training, holds as yet unconfirmed promise to aid recovery of key muscles (such as the diaphragm), to speed the process of ventilator weaning, and to truncate the PICS with acceptable safety. Unfortunately, strong clinical evidence supporting this logical approach remains lacking.

SUGGESTED READINGS


• Key Points

1. With little drug-targeted intervention, the outcome for most victims of poisoning is excellent. Supportive care, with particular attention to maintaining an airway, oxygenation, and perfusion, is the mainstay of treatment. Becoming fixated on the details of specific antidotal therapy can lead to disastrous consequences if basic support of oxygenation and perfusion is ignored.

2. Adults suffering from overdoses rarely give a complete and accurate description of the quantity or type of medications ingested. In most adult cases, multiple substances are involved.

3. A tentative diagnosis in most overdose and poisoning cases can be made by physical examination and simple laboratory tests (electrolyte profile, creatinine, serum osmolality, urinalysis, etc.).

4. Basic treatment principles include limiting the amount of toxin absorbed, enhancing elimination of absorbed toxin, and preventing conversion of nontoxic compounds to toxic metabolites.

5. Drugs or poisons for which specific antidotes or effective therapies exist (especially acetaminophen, salicylates, methanol, ethylene glycol, and digitalis) should be aggressively sought (including specific quantitative levels) and treated after initial stabilization has been accomplished.

Overdoses and poisonings account for approximately 15% of all intensive care unit (ICU) admissions, but most overdose patients do well and require only a brief stay. Despite myriad potential toxins, just a few account for more than 90% of all overdoses, with acetaminophen now being the single most common problem. Overall, most poisonings are oral ingestions: in adults, usually deliberate and involving multiple compounds, and in children, usually accidental intake of a single agent. Most poisonings occur in otherwise healthy young patients, which partially explains the low in-hospital mortality rate (approx. 1%). Most fatalities arise from arrhythmia, seizures, or hyperventilation-induced anoxic brain damage before patients reach the hospital or only shortly after arrival.

**DIAGNOSIS**

**Clinical History**

The clinical history is often erroneous. Many patients misstate the quantity of ingested drug; others have taken a medication they conceal, and the reported time of ingestion is often inaccurate. Suicidal patients may attempt to hide the type of poisons or drugs, and patients taking illicit drugs often lack accurate knowledge of what they took or fail to provide information, fearing prosecution. Occasionally, patients are victimized by surreptitious administration of a sedative or hypnotic agent of which they have no knowledge. In such cases, sexual assault is often the motive. Because patients may switch the contents of labeled bottles and accidental overdose may result from pharmacy dispensing errors, it is always wise to examine the contents of prescription bottles to ensure they match the label. It is important to seek the following information: (1) type of drug or toxin including ingestion of a sustained release form; (2) chronicity of use; (3) quantity consumed; (4) time elapsed since ingestion; (5) initial symptoms, including a history of vomiting or diarrhea; and (6) underlying diseases or other drugs taken.

**Physical Examination**

The physical examination is extremely valuable because it may allow rapid classification of patients into classic “toxic syndromes (toxidromes),” which can help in toxin identification and guide initial therapy. The cardinal manifestations of these syndromes and their common causes are illustrated in Table 33-1.

| Table 33-1. Major Toxic Syndromes
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<td>Signs and Symptoms</td>
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<tr>
<td>Temperature</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Reduced/Normal</td>
<td>Reduced/Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Pulse</td>
<td>Rapid</td>
<td>Rapid</td>
<td>Slow/Normal</td>
<td>Slow/Normal</td>
<td>Normal/Slow</td>
</tr>
<tr>
<td>Respiration</td>
<td>Normal</td>
<td>Rapid</td>
<td>Depressed</td>
<td>Normal/Depressed</td>
<td>Bronchorrhea/Wheezing</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Normal/Elevated</td>
<td>Elevated</td>
<td>Normal/Reduced</td>
<td>Normal/Reduced</td>
<td>Normal or Low</td>
</tr>
<tr>
<td>Eyes</td>
<td>Mydriasis</td>
<td>Mydriasis</td>
<td>Miosis</td>
<td>Normal</td>
<td>Miosis/Lacrimation</td>
</tr>
<tr>
<td>GI Tract Function</td>
<td>Decreased</td>
<td>Increased</td>
<td>Decreased</td>
<td>Normal</td>
<td>Diarrhea/Vomiting</td>
</tr>
<tr>
<td>Others</td>
<td>Seizures</td>
<td>Seizures</td>
<td>Hyporeflexia</td>
<td>Muscle weakness</td>
<td>Salivation</td>
</tr>
<tr>
<td></td>
<td>Myoclonus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The first steps in treating a patient with poisoning are to assess the vital signs and ensure an adequate airway, oxygenation, and perfusion. The airway of the overdosed patient may be obstructed, particularly if narcotics, sedatives, or caustic agents have been ingested. Intubation and artificial ventilation are required when there is airway obstruction or the central drive to breathe is depressed. Because respiratory drive may be unstable, and vomiting is common, noninvasive ventilation is usually a poor choice for support of the overdosed patient. As a general rule, a patient sedated enough to allow unresisted endotracheal intubation almost certainly requires the airway protection and ventilatory support the procedure provides. When it takes several people to restrain a combative patient, the need for intubation should be reconsidered, unless sedation is required for diagnostic evaluation (e.g., head computed tomography [CT] scan, lumbar puncture) or for protection of the patient or staff. Supplemental oxygen should be routinely administered to the poisoning victim until sustained adequacy of oxygenation can be confirmed by arterial blood gas data or pulse oximetry.

Hypoventilation is a clue to narcotic, sedative, tramadol, carisoprodol, clonidine, or gamma hydroxybutyrate (GHB) overdose. Recently, an industrial solvent, 1,4-butanediol, also known as GBL or GHV, with clinical effects similar to GHB, has grown in popularity as a cheap recreational drug. Hyperventilation due to central nervous system (CNS) stimulation should suggest salicylate, theophylline, amphetamine, phencyclidine (PCP), or cocaine toxicity. Hyperventilation can also result from toxin-induced metabolic acidosis as seen with metformin, methanol, ethylene glycol, or propofol or from tissue hypoxia caused by cyanide or carbon monoxide (see Chapter 40). Any compound that causes methemoglobinemia, such as dapsone, amide-containing topical anesthetics, and sulfonamides may also lead to hyperventilation.

Blood pressure and perfusion should be assessed and corrected rapidly if inadequate. Anticholinergic, cyclic antidepressant, or sympathomimetic (e.g., cocaine, amphetamine) poisoning should be suspected in patients with marked tachycardia. Sinus bradycardia or conduction system block may result from overdoses of digitalis, clonidine, β-blockers, calcium channel blockers, or other cholinergic drugs. Although hypertension is nonspecific, marked hypertension should suggest amphetamine, cocaine, thyroid hormone, methylendioxyemethamphetamine (MDMA, ecstasy), and catecholamine toxicities. Temperature may provide a valuable etiologic clue as well. Hyperthermia suggests anticholinergic, MDMA, amphetamine, or cyclic antidepressant poisoning or may be indicative of alcohol withdrawal, whereas hypothermia frequently accompanies alcohol or sedative-hypnotic overdose. (Hyperthermia can be seen in any overdose that leads to prolonged environmental exposure to cool temperatures.) Once the airway, breathing, and circulation are ensured, patients should be administered thiamine (100 mg) to avert the possibility of Wernicke encephalopathy. Hyperventilation can also result from toxin-induced metabolic acidosis as seen with metformin, methanol, ethylene glycol, or propofol or from tissue hypoxia caused by cyanide or carbon monoxide (see Chapter 40). Any compound that causes methemoglobinemia, such as dapsone, amide-containing topical anesthetics, and sulfonamides may also lead to hyperventilation.

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The head should be examined closely for clues to other causes of coma (e.g., head trauma, subarachnoid hemorrhage) and to provide data relevant to overdose. Inspection of the mouth may reveal unswallowed tablets or evidence of caustic injury. Breath odor may suggest a particular toxin (Table 33-2). For instance, ketones give a sweet odor, whereas cyanide presents an almond scent. The characteristic smell of hydrocarbons is distinguished easily, as is the "garlic" odor of organophosphate ingestion. Narcotics, barbiturates, organophosphates, and phenothenizines commonly produce miosis, whereas drugs with anticholinergic properties (e.g., amphetamines, antihistamines, ecstasy, cocaine, and cyclic antidepressants) cause mydriasis. Nyctagmus is often seen with ethanol, carbamazepine, PCP, or phenytoin ingestion. Lithium, volatile solvents, and prindomide also cause nyctagmus.) Pupils that appear fixed and dilated can result from profound sedative overdose but are characteristic of glutethimide or mushroom poisoning. Pupils that are dilated but reactive suggest anticholinergic or sympathomimetic poisoning. Because even the slightest reaction has positive prognostic implications, the pupillary response should be tested using a bright light in a darkened room. Hypeactive bowel sounds accompany narcotic or anticholinergic agents, whereas hyperactive bowel sounds may result from poisoning with organophosphates.

### Laboratory Testing

The electrocardiogram (ECG) can provide valuable clues in drug overdose. Ectopy is common in sympathomimetic and tricyclic poisoning. High-grade atrioventricular (AV) block may be due to digoxin, β-blockers, calcium channel blockers, cyanide, phentoin, or cholinergic substances. A wide QRS complex or prolonged QT interval suggests the effects of a variety of psychotropic, sedative, and anti-arrhythmic drugs.

Arterial blood gases are helpful to assess acidbase status and gas exchange and suggest salicylate intoxication if they reveal a mixed respiratory alkalosis and metabolic acidosis. Metabolic acidosis with compensatory hyperventilation is common with cyanide or carbon monoxide exposure (see also Chapter 40) and with the propofol infusion syndrome (PRIS).

In addition to arterial blood gas determinations, measurement of hemoglobin saturation and oxygen content by co-oximetry may be helpful. Both methemoglobin and carboxyhemoglobin lead to a disparity between the measured oxygen content or measured hemoglobin saturation and that predicted from the arterial oxygen tension (PaO₂). Carboxyhemoglobin is elevated by carbon monoxide poisoning, and a number of drugs including dapsone, benzocaine, and sulfonamides can oxidize hemoglobin to methemoglobin. Profound methemoglobinemia should be suspected in patients with dyspnea seemingly without or with little lung disease and may be recognized at the bedside by the chocolate brown color tinge it imparts to blood.

It is essential to calculate the anion and osmolar gaps. The numerical difference between the serum sodium and the sum of the chloride and bicarbonate is called the anion gap, and it normally ranges from 3 to 12 mEq/L. Six relatively common poisonings elevate the anion gap: (1) salicylates, (2) methanol, (3) ethanol, (4) ethylene glycol, (5) cyanide, and (6) carbon monoxide. Caution is advised, however, because hypoalbuminemia can reduce the anion gap, obscuring an important clue to overdose. (For each reduction in albumin concentration of 1 g/dL, the anion gap declines by an average of 2.5 mEq/L.)

The osmolar gap is the difference between the calculated osmolality and the osmolarity measured by a freezing point depression assay. When an osmolar gap greater than 10 mOsm exists, ethanol, ethylene glycol, isopropanol, and methanol become the most likely offenders; however, any unmeasured osmotic substance (e.g., glyceral, mannitol, sorbitol, radiopaque agents, acetone, glyline) can widen the osmolar gap. Ketosis suggests ethanol, paraldehyde, or diabetes as potential culprits, although in many cases, simply not eating (starvation ketosis) is the explanation for mild ketosis. If ketones are present without systemic acidosis, isopropyl alcohol is the probable etiology.

Hypocalcemia is produced by the ingestion of ethylene glycol, oxalate, fluoride compounds, and certain rare metals: manganese, phosphorus, and barium. On rare occasions, chest or abdominal radiographs may help identify radiopaque tablets of iron, phenothenizines, tricyclic agents, or chloral hydrate. When these drugs are involved, the abdominal radiograph may help to ensure that the gut has been emptied after emesis or gastric lavage.

### Use of the Drug Screen

Most qualitative drug screens assay urine or blood using thin-layer chromatography. Because there is no "standard" for which substances are included in a drug screen, it is important to know which compounds are assayed in each hospital. Urine and gastric juice are the most reliable samples for toxin assay because many common drugs (e.g., aspirin, acetaminophen, ethanol, methanol, ethylene glycol, GHB) are omitted from "routine" screens, and tests for each must be requested specifically. If a particular toxin is suspected, specific assay techniques may provide more rapid and quantitative results. A negative screen alone does not exclude overdose because of problems with sensitivity and timing of the test in relation to ingestion. In other cases, the screen does not detect the offending agent (e.g., fentanyl). In some screening assays, commonly used drugs may be reported as the presence of a suspected toxin because of cross-reactivity (Table 33-3).

Whenever there is doubt regarding drug screen results, clinical judgment should prevail. Specific therapy is available for certain toxins for which quantitative levels should be obtained to guide management (Table 33-4).

<table>
<thead>
<tr>
<th>False Positive</th>
<th>False Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>Ranitidine</td>
</tr>
<tr>
<td></td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td></td>
<td>Bupropion</td>
</tr>
<tr>
<td></td>
<td>Selegiline</td>
</tr>
<tr>
<td></td>
<td>Amphetamines</td>
</tr>
<tr>
<td></td>
<td>Pseudoephedrine</td>
</tr>
</tbody>
</table>
### Table 33-4. Compounds for Which Quantitative Assay is Helpful

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Digitalis</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Methanol</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Salicylates</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>Carbon monoxide</td>
</tr>
<tr>
<td>Iron</td>
<td>Lithium</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Methemoglobin</td>
</tr>
<tr>
<td>Lead</td>
<td>Most anticonvulsants</td>
</tr>
</tbody>
</table>

*The authors acknowledge the input of Dr. Sean Boley and the Regions Hospital Toxicology Program in revision of this table.*

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**TREATMENT OF DRUG OVERDOSE**

Physiologic support is key to all overdose management. Three basic precepts help minimize the toxic effects of drug ingestion: (1) prevent additional toxin absorption, (2) enhance drug removal, and (3) prevent formation of toxic metabolites. Depending on the drug ingested, appropriate therapy also may include antidote administration or toxin removal.

#### Prevention of Toxin Absorption

After initial stabilization, the next step in the treatment of poisoning is to stop absorption. For cutaneously absorbed toxins (e.g., organophosphates, nerve agents), removing contaminated clothing and washing the skin is particularly important. Contaminated clothing needs to be placed in sealed bags and safely disposed of to avoid secondary exposure and incapacitation of health care workers. Such precautions are particularly important if dealing with potent nerve toxic agents that are used in terrorist attacks.

For ingested toxins, induction of emesis is rarely, if ever, indicated. Long delays between ingestion and hospital presentation limit emesis effectiveness, and for patients with altered mental status or suppressed gag reflex, vomiting is dangerous. Emesis is not appropriate in ingestion of corrosive chemicals or petroleum distillates.

In adults, gastric lavage may be performed via a large-bore tube inserted orally, using serial aliquots of 100 to 200 mL of normal saline or water. Studies have failed to confirm consistent outcome benefit from lavage, even if performed soon after the poisoning. Current recommendations suggest that gastric lavage not be used routinely and that it be considered only in life-threatening cases when it can be undertaken within 1 hour of ingestion. The airway must be protected in patients with a depressed level of consciousness. Lavage is contraindicated in acid or alkali ingestions because of possible esophageal perforation and is advisable when bleeding risk is significant. Complications of lavage include aspiration pneumonitis, esophageal perforation, and cardiovascular instability.

Activated charcoal (usually 1 g/kg) can be given to absorb orally ingested drugs (Fig. 33-1). The greatest benefit occurs when charcoal is given within 1 hour of ingestion. Although serious risks are small, activated charcoal frequently causes vomiting and may produce localized pneumonitis or acute respiratory distress syndrome (ARDS).
when aspirated. Charcoal presents an enormous absorptive area (>1,000 m$^2$/g) and binds many toxins within minutes of administration; however, activated charcoal is not
effective in reducing the toxic effects of many common poisons (Table 33-5). Substances not absorbed by activated charcoal include iron, lithium, cyanide, strong acids or
bases, alcohols, and hydrocarbons. The only clear contraindication to giving charcoal is known or suspected gastrointestinal tract perforation.

The once popular use of single-dose activated charcoal for nearly all toxic ingestions has fallen out of favor with the realization that in most cases, sufficient time has
lapsed to preclude benefit, whereas risks remain. Although charcoal tends to constipate, cathartics may deplete fluids and electrolytes, and repeated doses are not
routinely needed unless large volumes or multiple doses of activated charcoal are given. Bowel obstruction can result from retention of charcoal in the colon. Sorbitol is
the preferred cathartic because it works faster than does magnesium citrate and avoids the magnesium toxicity that can result if renal function is impaired. Other
absorbents such as bile acid sequestrants (e.g., cholestyramine) also can be used to reduce absorption of specific agents such as thyroid hormone and compounds with
significant enterohepatic circulation.

Another method to decrease toxin absorption is whole bowel irrigation, in which vigorous catharsis
is produced using a polyethylene glycol solution. Approximately 1 to 2 L of the solution is drunk (or instilled via gastric tube) each hour until the rectal effluent is clear of
pill fragments (typically 3 to 5 hours). Whole bowel irrigation is most useful when clearing sustained-release drugs and in cases of "body packing," where packages of
ingested illicit drugs may rupture with fatal consequences. Bowel irrigation requires a nonobstructed GI tract and works best with an alert, cooperative patient.

Enhancement of Drug Removal

Four therapeutic techniques enhance removal of circulating toxins: (1) gut dialysis, (2) ion trapping, (3) hemodialysis, and (4) hemoperfusion. Drugs undergoing
enterohepatic circulation, such as theophylline, digoxin, phenobarbital, dapsone, and carbamazepine, may be eliminated by "gut dialysis," a process using repeated doses
of oral activated charcoal to bind drug excreted into the bile. Although the effectiveness of multiple-dose charcoal is poorly studied, three or four doses of 0.5 to 1 g/kg
given every 2 to 4 hours have been advocated.

Charged molecules do not cross lipid membranes easily; therefore, ionized drugs are not absorbed readily from the stomach and fail to cross the blood-brain barrier.
Furthermore, once in the renal tubule, such molecules have a limited tendency to back-diffuse into the circulation. Because urinary pH can only be altered between values

### Table 33-5. Poisons Not Absorbed by Activated Charcoal

<table>
<thead>
<tr>
<th>Substance</th>
<th>Activated Charcoal</th>
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</thead>
<tbody>
<tr>
<td>Acids</td>
<td>Alkalis</td>
</tr>
<tr>
<td>Iron</td>
<td>Lithium</td>
</tr>
<tr>
<td>Organophosphates</td>
<td>Carbamates</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>Alcohols</td>
</tr>
<tr>
<td>Potassium</td>
<td>Heavy metals</td>
</tr>
<tr>
<td>Hydrocarbons</td>
<td>Cyanide</td>
</tr>
</tbody>
</table>

*The authors acknowledge the input of Dr. Sean Boley and the Regions Hospital Toxicology Program in revision of this table.*
of the serum and urine, although often difficult to achieve, can impede transfer of weak acids (e.g., salicylates, cyclic antidepressants, phenobarbital, methotrexate, and isoniazid) and promotes their excretion. Sodium bicarbonate (88 to 132 mEq) can be added to a 1-L solution of 5% dextrose in water, with the rate of administration determined by the patient's ability to handle the fluid load and maintain urine pH greater than 7. Hypokalemia often requires correction to achieve urinary alkalization. Hypokalemia is most effective when minute ventilation is also controlled; hyperventilation in response to the induced metabolic alkalosis can impair the ability to achieve alkalemia. Hypokalemia must be avoided; not only does hypokalemia predispose to arrhythmias, but also it impairs the ability to achieve an alkaline urine by promoting hydrogen ion secretion as potassium is reabsorbed in the distal tubule. The carbonic anhydrase inhibitor acetazolamide should not be used to alkalize the urine because it results in acidemia and can worsen drug toxicity of some poisons (i.e., salicylates, tricyclic antidepressants).

Urinary acidification using arginine, lysine, or ammonium chloride may accelerate excretion of weak bases such as amphetamine, strychnine, PCP, and quinidine. The practice is questionable effective and potentially dangerous for patients with renal or hepatic dysfunction and may exacerbate myoglobinuric renal injury.

Dialysis should be considered for life-threatening ingestions involving water-soluble substances of low molecular weight. Drug overdoses in which dialysis may be beneficial include alcohols, amphetamines, phenobarbital, lithium, salicylates, theophylline, thiocyanate and valproic acid. Hemoperfusion is useful for a variety of compounds; it involves passing blood through a filtering device that contains charcoal or a synthetic resin as an absorbent. Charcoal hemoperfusion may be preferred over dialysis for eliminating carbamazepine, phenobarbital, phenytoin, and theophylline. Hemodialysis and hemoperfusion efficiently remove poisons but are costly and may be associated with complications. Use of continuous hemodialysis and hemoperfusion techniques in poisoning has been reported on a limited basis. Continuous techniques may be an option in hemodynamically unstable patients. Hemofiltration has theoretical attractiveness to extract compounds with large volumes of distribution, extensive tissue binding, or slow intercompartmental transfer.

**Inhibition of Toxic Metabolite Formation**

Some drugs, most notably acetaminophen, methanol, and ethylene glycol, are relatively inert when ingested but form highly toxic compounds during metabolism. Inhibition of toxin formation will be discussed later under specific therapy for these poisons.

**SPECIFIC POISONS**

**Acetaminophen**

Acetaminophen is safe when taken in recommended doses, but ingestion of as little as 6 g may be fatal. (Usually, a fatal dose exceeds 140 mg/kg.) Fortunately, not all acetaminophen overdoses are life threatening and do not require specific therapy. Acetaminophen is absorbed within 1 hour, especially when taken in the liquid form. The usual serum half-life is approximately 2 to 4 hours but lengths with declining liver function. Normally, the drug is metabolized hepatically to nontoxic compounds by linkage with sulfates and glucuronide. The hepatic cytochrome P-450 system converts less than 5% of an ingested dose to reactive metabolites, which are then detoxified by conjugation with glutathione. However, during massive overdose, toxic metabolites (N-acetyl-p-benzoquinoneimine) overwhelm the glutathione supply and accumulate to cause liver damage. Conditions that induce the hepatic cytochrome P-450 system, including chronic use of ethanol, oral contraceptives, or phenobarbital, predispose to toxicity.

Even in serious acetaminophen overdose, symptoms are minimal for the first 24 hours after ingestion, with the exception of nausea and vomiting. One to two days after ingestion, deteriorating liver function tests, right upper quadrant pain, and oliguria (because of the antidiuretic hormone-like effects of acetaminophen) become evident. At this time, hepatic transaminases may peak in the tens of thousands of units. Hepatic necrosis and failure evolve within 3 to 5 days. (This toxicity is often manifested by a rising bilirubin level and prothrombin time and declining transaminases.) In this most advanced stage, mental status declines and renal failure develops. If the patient is to recover, improvement is typically noted between days 5 and 7. Poor prognostic factors include late presentation and the presence of coagulopathy, metabolic acidosis, renal failure, and cerebral edema.

In addition to hemodynamic and respiratory support, if care is initiated soon after ingestion, initial treatment should include evacuation of the stomach and administration of activated charcoal. Charcoal reduces absorption of acetaminophen, potentially averting a toxic serum level; a specific antidote, N-acetylcysteine (NAC), is the drug of choice. Not all patients require therapy with NAC; the likelihood of hepatic toxicity from an isolated acute ingestion may be predicted from a standard (Rumack-Matthew) nomogram using the serum level obtained more than 4 hours after ingestion. Patients with preexisting chronic use of substances or liver disease may develop symptoms at concentrations much lower than the nomogram predicts. For such patients, it makes sense to begin NAC therapy if acetaminophen levels exceed 10 μg/mL, or hepatic transaminases demonstrate any elevation. For patients who ingest extended-release preparations, it makes sense to obtain serial levels at 4- to 6-hour intervals after ingestion. If any level reaches the toxic threshold, therapy should be undertaken. NAC probably has a twofold action: directly binding the toxic metabolites of acetaminophen and repleting intracellular glutathione. For maximal effectiveness, NAC should be given as quickly as possible. Historically, treatment has included an oral loading dose of 150 mg/kg over 60 minutes followed by 50 mg/kg infused over 4 hours and then 100 mg/kg infused over 16 hours. Anaphylactoid reactions have been reported during intravenous N-acetylcysteine in approximately 15% of patients. When NAC is given orally, vomiting is so common that “prophylactic” antiemetic therapy should probably be administered. Intravenous NAC, free of emetogenic effects, is now available, and short-duration infusions (24 hours) are safe, cost-effective, and at least as effective as the older, less-convenient oral regimen. (Intravenous therapy is rarely associated with flushing or angioedema.) Of note, liver injury induced by acetaminophen commonly predisposes patients to hypoglycemia, which should be closely monitored and treated. When massive hepatic necrosis develops, liver transplantation may be considered if irreparable brain injury has not occurred from hepatic failure-induced cerebral edema.

**Salicylates**

Salicylate overdoses are now uncommon but continue to be highly lethal. Up to one third of all salicylate intoxication victims die before leaving the emergency department, often arriving in extremis. In large doses, salicylates inhibit cellular enzymes and uncouple oxidative phosphorylation. The clinical presentation of salicylate overdose includes altered mental status, tinnitus, acidosis, and hypoxia and (more rarely) hyperosmolality, hyperthermia, and seizures. Salicylate intoxication can easily be confused with a psychotic episode. Initially, direct CNS stimulation causes a respiratory alkalosis and compensatory renal wasting of bicarbonate. Later, superimposed metabolic acidosis may produce a complex acid-base disturbance. Tachypnea may be absent if the patient has ingested a sedative or hypnotic concurrently. Large doses of aspirin may induce pulmonary edema, causing ARDS.

It does not take much aspirin to produce toxicity; a lethal adult dose ranges from 10 to 30 g (150 mg/kg). Salicylate intoxication always should be considered in the differential diagnosis of an anion gap acidosis. The anion gap elevation results primarily from lactate and pyruvate generated during anaerobic glycolysis, but ketones also are formed in response to decreased glucose and accelerated lipolysis. Very high serum salicylate levels (>80 mg/dL) may directly contribute to the anion gap. In addition, large insensible fluid losses deplete intravascular volume, thereby stimulating aldosterone secretion, which depletes bicarbonate and potassium. Salicylate levels higher than 50 mg/dL commonly induce nausea and vomiting and may produce a metabolic acidosis, leading to a “triple” acid-base disorder.

Salicylates inhibit the formation of prothrombin, impair platelet function, and irritate the gastric mucosa—all of which contribute to the risk of hemorrhage. Patients with salicylate-induced coagulopathy or bleeding should receive vitamin K and, if immediate reversal is necessary, fresh frozen plasma and platelets.
If therapy is to prevent morbidity, salicylate intoxication must be suspected on clinical grounds. In chronic toxicity, serum levels correlate poorly with toxicity, but in acute intoxication, adverse effects are uncommon with serum levels below 35 mg/dL. Moderate toxicity often is seen with acute ingestions of 150 to 300 mg/kg. Another salicylate preparation, oil of wintergreen, represents a significantly greater risk; one teaspoon provides the amount of salicylate in almost 20 aspirin tablets (7 g). In acute salicylate poisoning, initial levels above 120 mg/dL, 6-hour levels higher than 100 mg/dL, or any level greater than 500 mg/dL is associated with a high risk of death. Declining salicylate levels should not necessarily be reassuring, as they may merely indicate transit of the salicylate from the plasma to tissue.

Because salicylates are rapidly absorbed, at the time of presentation, it is almost always too late for effective gastric evacuation. However, in massive overdoses, serum levels may continue to rise for up to 24 hours after ingestion because of delayed gastric absorption. As weak acids, salicylates remain nonionized at low serum pH and readily cross cell membranes; therefore, ion trapping with bicarbonate may be used to lower toxicity and promote excretion. In addition to decreasing urinary excretion, an acidic pH favors movement of salicylates into cells and across the blood-brain barrier. Therefore, serum and urine pH should be monitored and kept alkaline with bicarbonate titration or dialysis. Development or worsening of acidosis can lead to a precipitous clinical decline. An example of this phenomenon occurs when a patient hyperventilating to compensate for metabolic acidosis is sedated and/or paralyzed for intubation; the lower postintubation minute ventilation can result in an abrupt decompensation as salicylate shifts from plasma to cells. Hemodialysis is indicated for severe intoxications. When patients are known to have acutely ingested massive doses (>30 g), when serum levels exceed 100 mg/dL, or when coma, seizure, renal failure, or pulmonary edema occurs, dialysis should be considered.

Stimulants

Stimulants exert their toxicity through direct CNS excitation or by causing catecholamine release, inhibiting catecholamine reuptake, or by inhibiting monoamine oxidase. Patients experiencing stimulant (amphetamine, ecstasy [XTC, MDMA], cocaine, and PCP) overdose characteristically present with agitation, hypertension, tachycardia, mydriasis, and warm, moist skin. Occasionally, rhabdomyolysis, hyperkalemia, and seizures occur. Vertical nystagmus is a common feature in PCP intoxication, whereas hyperthermia and hyponatremia (from inappropriate ADH secretion and excessive water intake) may be more common with ecstasy. Cardiac ischemia induced by the vasoconstrictive and chronotropic effects of cocaine may cause acute myocardial infarction, even in young patients and those without coronary artery disease. Aortic dissection (occasionally painless) also occurs with cocaine intoxication with several case reports of acute paraplegia as spinal cord blood supply is disrupted. Therefore, in cocaine intoxications, an ECG should be obtained, and if suspicious, myocardial ischemia or injury should be confirmed or excluded by serial ECGs and cardiac enzyme determinations. Treatment of myocardial ischemia associated with cocaine intoxication should not differ from that of conventional acute coronary syndromes. A low threshold to perform computed tomograms of the chest and abdomen should be maintained in patients with symptoms suggestive of dissection. The vasculature of the brain is also susceptible to the effects of cocaine resulting in ischemic and hemorrhagic strokes and subarachnoid hemorrhage. When smoked, cocaine base can cause a syndrome of pulmonary hemorrhage leading to acute respiratory failure known as “crack lung.” However, even in the absence of alveolar damage, crack smoking is now a frequent cause of exacerbations of obstructive lung disease.

For most stimulant overdoses, specific treatment is lacking; however, maintenance of the airway, oxygenation, and control of blood pressure are universally indicated. Providing adequate hydration to maintain urine flow is important because many compounds in this class may precipitate rhabdomyolysis. Agitation can be controlled with benzodiazepines. Perhaps the best first treatment for the hypertension associated with stimulant ingestion is a benzodiazepine. Hypertension and tachycardia that persist after sedation can be managed with any number of vasodilators, with or without a β-adrenergic blocker. In this setting, the use of β-blockers alone is discouraged because of the possibility of unmasking unblocked α-agonist effects. Thus, labetalol is a good choice among vasoactive drugs as it blocks both α- and β-receptors.

Alcohols

Ethanol

Many suicide attempts involve ethanol, either alone or in combination with other drugs. Physiologic effects do not relate closely to serum concentrations, but blood levels higher than 150 mg/dL are inebriating. Coma usually requires levels higher than 300 mg/dL, and death rates rise when concentrations exceed 600 mg/dL. The therapy of acute alcohol intoxication is largely supportive. Administration of thiamine and folate with correction of serum glucose, potassium, and magnesium levels is indicated. Ethanol may be quickly removed by hemodialysis, an intervention that is rarely necessary. The ICU deprives the habituated patient of ethanol access. Deprivation may precipitate withdrawal, a condition that is significantly more dangerous than intoxication. Symptoms of withdrawal usually start within 36 hours of the last drink (but may be delayed for 5 to 7 days). Measurable serum levels of ethanol do not exclude the diagnosis of withdrawal. Patients experiencing severe withdrawal (hallucinations, delirium tremens [DT], etc.) are unpredictable, both in behavior and disease course. DT is the most extreme form of ethanol withdrawal, profoundly altering mental status and initiating lifethreatening autonomic instability. Therefore, most patients with DT should be managed in an ICU to avert or quickly respond to such potentially fatal complications as seizures, aspiration, arrhythmias, and suicide attempts. Symptoms of withdrawal (specifically DT) often mimic infection or primary neurologic processes. It is important to emphasize, however, that 50% of febrile patients with DTs also have a concomitant infection, most frequently pneumonia or meningitis. The agitated withdrawal patient should be restrained in a lateral or prone position (not supine because of the risk of aspiration). Patients should be given nothing by mouth (NPO); all fluids, electrolytes, and vitamins (B12, thiamine, folate, etc.) should be administered intravenously. Withdrawal may be prevented or aborted in its early stages through the use of oral benzodiazepines, but if fully manifest, intravenous lorazepam becomes the sedative of choice. Benzodiazepines reduce hyperexcitability and the risk of seizures. In this situation, intravenous benzodiazepines should be given frequently, in small doses, until the patient is calm but not obtunded. Haloperidol may be a useful adjunct. After initial control with intravenous dosing is achieved, oral maintenance therapy should be instituted. Lorazepam has become a popular choice because it is a long-acting drug available in both oral and intravenous forms, it does not require hepatic metabolism, and it has no active metabolites, a particularly useful property in patients with liver disease. Titratable β-blockers (e.g., esmolol) may also be helpful in well-selected hypermetabolic, tachycardiac patients. Labetalol is a better choice if the patient is also hypertensive.

<table>
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<th>Table 33-6. Features of Various Alcohol Intoxications</th>
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<td><strong>Ethanol</strong></td>
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<td>Osmolar gap</td>
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<td>Ketones</td>
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<td>Acidosits</td>
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Methanol and Ethylene Glycol Toxicity

A tabular overview of the clinical and laboratory features of the most common alcohol poisonings is presented in Table 33-6. The toxicity of methanol and ethylene glycol results from the formation of organic acids from the parent compounds. Toxic metabolites of ethylene glycol include oxalic, glycolic, and glyoxylic acids. Formic acid and formaldehyde are responsible for methanol toxicity. Formation of toxic metabolites of both compounds is delayed by concomitant ethanol ingestion. Methanol is found in paint remover, windshield deicing fluid, fuel line antifreeze, and canned solid fuel, whereas ethylene glycol is the major component of automobile antifreeze. Tiny amounts of these compounds are needed to produce life-threatening toxicity: 30 mL of methanol or 100 mL of ethylene glycol may cause severe injury.

Early methanol or ethylene glycol ingestion resembles ethanol intoxication. However, as symptoms progress, almost any global CNS finding may be seen, including coma, hypertonia, nystagmus, or seizures. Although the presentations of ethylene glycol and methanol are often indistinguishable, cardiovascular signs (tachycardia, hypertension, and pulmonary edema) and renal failure resulting from oxalate crystalluria more frequently complement ethylene glycol. On the other hand, optic neuritis and blindness are hallmarks of methanol poisoning. Methanol or ethylene glycol ingestion should be suspected in patients with acidosis and coexistent anion and osmolar gaps. Absence of a wide osmolar gap should not dissuade clinicians from the diagnosis in patients with delayed presentation because these parent alcohols are relatively rapidly cleared from the circulation while their toxic breakdown products continue to circulate. Specifically, lethal levels of ethylene glycol may be present with minimal elevations in the osmolar gap.

Treatment of ethylene glycol and methanol intoxication includes maintenance of a secure airway and administration of activated charcoal if other ingested substances are suspected. Activated charcoal does not absorb alcohols. The hypoglycemic patient should receive 50% glucose, thiamine, folate, and multivitamins. Folinic acid (leucovorin) 50 mg IV every 4 to 6 hours for 24 hours is indicated in methanol ingestion to provide the cofactor for formic acid elimination. These patients must also be hydrated sufficiently to maintain urine output. Ethylene glycol is excreted by the kidneys.

Ethanol or fomepizole can inhibit the metabolism of ethylene glycol and methanol, a process that requires alcohol dehydrogenase. Ethanol orally or intravenously is dosed to maintain a blood level of 100 to 150 mg/dL and competes with these toxic alcohols for breakdown to their injurious by-products. A loading dose is followed by a maintenance infusion. Increased dosing is required during hemodialysis. Fomepizole (4-methylpyrazole), a competitive inhibitor of alcohol dehydrogenase that does not cause CNS depression, is usually a better option than ethanol infusion. It is administered as a 15-mg/kg loading dose followed by 10 mg/kg every 12 hours for four doses and then 15 mg/kg every 12 hours until alcohol levels are decreased, acidosis is resolved, and the patient is asymptomatic. Fomepizole dosing must be adjusted during hemodialysis.

Early hemodialysis is instituted for a history suggestive of ingestion in the presence of a significant metabolic acidosis. Other indications include visual impairment, renal failure, pulmonary edema, and ethylene glycol or methanol level greater than 25 mg/dL. Hemodialysis removes the alcohol and toxic metabolites in addition to correcting acid-base status. Although bicarbonate can be useful as a temporizing intervention for management of acidosis in unstable patients until more effective measures are initiated, large volumes of bicarbonate may result in fluid overload or hyperosmolality.

Isopropyl alcohol is more intoxicating than ethanol and results in similar clinical characteristics at lower doses. Hand sanitizers may contain isopropyl alcohol in concentrations greater than 60%. Isopropyl alcohol ingestion is characterized by an osmolar gap and ketone production, but no metabolic acidosis. Treatment consists of gastric evacuation of the stomach and multidose charcoal potentially beneficial, even if undertaken hours after ingestion. Although lethargy, tachypnea, and dyspnea are hallmarks of methanol poisoning, it is important to recognize that patients treated with charcoal may still become comatose and require intubation and mechanical ventilation.

<table>
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<th>Visual changes</th>
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<tr>
<td>Ca²⁺ oxalate crystals</td>
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Sedative-Hypnotic-Analgesic Drugs

Barbiturates, benzodiazepines, and opioids are the most common sedating agents resulting in drug overdose. GHB is an increasingly popular drug of abuse but presents special challenges to diagnosis. Most sedative drugs depress consciousness and, in large doses, act as negative inotropes and vasodilators—occasionally causing cardiovascular collapse.

The benzodiazepines, however, have a wide therapeutic range, and when taken alone, doses of 50 to 100 times the usual therapeutic dose may still be well tolerated. Unfortunately, ethanol and opiates, common co-ingestants, accentuate toxicity. Benzodiazepines depress consciousness, reflexes, and respiration. Treatment consists of gastric evacuation for patients seen very shortly after ingestion, but for most, treatment is only supportive. There is no benefit to dialysis. Flumazenil is a competitive receptor antagonist that reverses the respiratory and central depressant effects of benzodiazepines in approximately 80% of patients.

High doses of benzodiazepines, long duration of therapy, and concomitant narcotic use lower the rate of reversal. Flumazenil has no beneficial effect on ethanol, barbiturate, narcotic, or tricyclic antidepressant-induced CNS depression. Because the liver clears flumazenil rapidly, its duration of action is substantially shorter than that of most benzodiazepines. Akin to the naloxone-opioid story, as many as 10% of patients given flumazenil relapse into a sedated state, making careful observation essential. When used, intermittent doses of 0.2 mg at over 30 seconds followed by doses of 0.3 and 0.5 mg every minute (up to 3 mg in total) are typical. Although sometimes helpful in establishing a diagnosis, flumazenil should be used cautiously because it may precipitate withdrawal symptoms (agitation, vomiting, and seizures), especially in chronic users of cyclic antidepressants or benzodiazepines. Flumazenil is expensive, is rarely needed in the ICU, and should be regarded as no more than an adjunct to airway protection and ventilation in the management of benzodiazepine overdose.

GHB (gamma hydroxybutyrate) is a natural metabolite of gamma-aminobutyric acid, which was banned in the United States in 1991 because of toxicity. Clinical effects with ingestion include initial euphoria, hypothermia, loss of consciousness, coma, respiratory depression, seizure-like activity, bradycardia, hypotension, and death. Coincident use of alcohol results in synergistic CNS and respiratory effects. More recently, chemical precursors of GHB have been abused with manifestations similar to GHB. Activated charcoal is unlikely to be of benefit because these drugs are rapidly absorbed. Patients usually recover spontaneously within hours, but supportive therapy with airway protection and mechanical ventilation may be necessary during this time. A prolonged GHB withdrawal syndrome with agitation and delirium has been reported in high-dose frequent users.
The predominant toxicity of opioids (e.g., morphine, heroin, fentanyl, methadone, meperidine, pentazocine, propoxyphene, and diphenoxylate) is depression of consciousness and respiration. Aspiration pneumonitis is a common complication. Hypothermia, decreased gut motility, noncardiogenic pulmonary edema, and seizures (most common with propoxyphene and meperidine) can also be seen. Status epilepticus should raise the possibility of a massive overdose as sometimes seen in heroin “body packers.” Although most opioids are ingested or injected, fentanyl is readily absorbed through the skin and is available transcutaneously. Hence, for all patients presenting with suspected sedative overdose, a careful examination for fentanyl patches should be conducted. All opioids can be detected on routine urine toxicology screens with the exception of fentanyl, which may require special blood analysis.

Organophosphates and Carbamates

Organophosphates and the related carbamate insecticides inhibit the action of acetylcholinesterase, thereby causing accumulation of acetylcholine at neuromuscular junctions. Early specific treatment is important because binding of the toxin to acetylcholinesterase may become irreversible after 24 hours. Organophosphates initially stimulate but later block acetylcholine receptors. Organophosphates penetrate the CNS, but carbamates do not. Toxic manifestations usually appear within 5 minutes (especially after inhalation) but may be delayed for 24 hours when exposure is cutaneous or enteral. Muscle weakness resulting from organophosphate poisoning can persist for weeks. This syndrome is uncommon in the United States but is seen more commonly in developing countries. Worldwide, an estimated 5 million people are exposed to these compounds annually. Mortality rate has been estimated at approximately 10%.

Nerve gases such as sarin, which could be used in terrorist attacks, produce similar toxicity. These compounds are absorbed through the skin, lungs, and gut and bind to acetylcholinesterase, rendering it nonfunctional. Acetylcholine accumulation at cholinergic receptors results in typical cholinergic toxicity.

Cholinergic poisoning exerts potential deleterious effects on three systems. First is the muscarinic or parasympathetic system, causing bronchorrhoea, bradycardia, and SLUDGE (satiation, lacrimation, urination, defecation, gastrointestinal upset, emesis) syndrome. Second is the nicotinic autonomic system, resulting in muscle weakness. Third, CNS dysfunction includes confusion, slurred speech, and central respiratory depression. Pulmonary toxicity from bronchorrhoea, bronchospasm, and respiratory depression is the major concern.

Onset of symptoms depends on the route of exposure and the specific agent. Oral and respiratory exposures elicit a more rapid onset of symptoms (within 5 minutes) than a skin-only exposure (up to 12 hours). The more lipophilic agents are associated with delayed onset of symptoms as well as a more prolonged course of illness. Organophosphate inactivation of acetylcholinesterase lasts for days to weeks. Carbamate toxicity is generally of shorter duration (1 or 2 days) than organophosphate toxicity and results in temporary inactivation of acetylcholinesterase. Nonetheless, mortality rates are similar to toxicity from exposure to organophosphates.

Both IV atropine and pralidoxime are indicated for management of these poisonings. If there are no CNS symptoms, glycopyrrolate may be substituted for atropine. Atropine exerts its effect by competing with acetylcholine at muscarinic receptors. Large amounts of atropine may be required, with initial doses usually 2 to 4 mg IV repeated every 2 to 5 minutes. Intramuscular administration may be considered emergently when IV access is not available.

A continuous infusion of atropine started at 0.5 mg/kg/h titrated to clinical effectiveness may be necessary. The endpoint of atropine use is clearing of secretions from the tracheobronchial tree.

Atropine does not reverse nicotinic manifestations. Therefore, patients with substantial respiratory muscle weakness require the use of pralidoxime. Pralidoxime combines irreversibly with organophosphates, freeing acetylcholinesterase if given early enough (usually <48 hours after exposure). Acetylcholinesterase activity may be restored provided that the organophosphate-acetylcholinesterase complex did not age to the point of rendering acetylcholinesterase resistant to reactivation. Pralidoxime is usually administered as an initial bolus of 1 to 2 g over 30 minutes and then maintained as a continuous infusion (200 to 500 mg/h) maintained as long as atropine is continued. An intermediate syndrome of respiratory paralysis, bulbar weakness, proximal limb weakness, and decreased reflexes may develop 24 to 96 hours after resolution of the cholinergic crisis. This intermediate syndrome is almost always the result of organophosphate poisoning rather than carbamate exposure. Recovery may take several weeks.

Digitalis Compounds
All of the symptoms of digitalis glycoside poisoning are nonspecific (fatigue, weakness, nausea, visual complaints, etc.) and are common in the elderly population with cardiac disease. Therefore, a low threshold of suspicion must be maintained for digitalis toxicity. Vigilance is especially necessary because the frequency of digitalis use has declined significantly. Renal insufficiency, hypothyroidism, heart failure, and electrolyte abnormalities (e.g., hypokalemia and hypomagnesemia) predispose patients to digitalis toxicity. Initiation of calcium channel blockers, type la antiarrhythmics, or amiodarone also can precipitate digitalis toxicity. The major toxicity of digitalis compounds is hyperkalemia and associated arrhythmias (AV nodal block and increased automaticity) resulting from poisoning of the cellular sodium-potassium pump.

Treatment consists of activated charcoal to decrease drug absorption and normalization of serum magnesium and potassium levels. Atropine and pacing are indicated for severe bradycardia. Lidocaine and phenytoin are the drugs of choice for ventricular tachycardia. It is best to avoid quinidine, β-blockers, and calcium channel blockers. Specific therapy using highly purified ovine IgG-Fab antibody fragments (e.g., Digibind) is indicated for digoxin levels greater than 6 ng/mL, when potassium exceeds 5.5 mEq/L, or when refractory tachycardia or bradycardia occur. The usual adult dose of 10 to 20 vials in acute toxicity produces a response within 30 minutes. In chronic toxicity, 6 vials may be recommended. Digitalis antibody fragments are very safe—theyir only recognized toxicities are due to the reversal of digitalis effects (i.e., hypokalemia, congestive heart failure, and rapid ventricular response to atrial fibrillation). Because the antibody fragment-digitalis complex is detected by digoxin assays, plasma levels are not valid after antibody administration. With normal renal function, digitalis antibodies are cleared rapidly (46 to 72 hours), but clearance is reduced dramatically by renal insufficiency.

Cyclic Antidepressants

Cyclic antidepressant use has declined significantly with the popularity of serotonin reuptake inhibitors (SSRIs), but they remain a common cause of drug overdose because they are used widely for depression, pain, and sleep, have a long half-life, and accumulate in the tissue. Despite the frequency of cyclic antidepressant overdoses, in-hospital mortality remains below 1% with most deaths occurring in the prehospital phase of illness or shortly after admission. Signs of cyclic antidepressant overdose are predominantly anticholinergic. The mnemonic phrase “hot as a hare, blind as a bat, dry as a bone, red as a beet, mad as a hatter” accurately describes severely intoxicated patients, who often demonstrate hyperthermia, fixed and dilated pupils, dry red skin, and CNS hyperactivity (hallucinations and psychosis). Patients with lesser degrees of intoxication have predominantly CNS sedation. The differential diagnosis of cyclic antidepressant overdose includes other compounds having anticholinergic effects (e.g., atropine, antihistamines, phenothiazines, scopolamine, anti-Parkinson drugs, jimson weed, and mushroom poisoning).

Because of their tendency to produce ileus, cyclic antidepressants may remain in the gut long after ingestion; therefore, gastric evacuation and oral charcoal can be effective in limiting toxicity. Toxicity correlates poorly with ingested dose or serum level because of the high tissue affinity.

The ECG warns of cardiac (and CNS) toxicity when the QRS complex in limb leads extends beyond 0.10 seconds. In such patients, the QTc and PR intervals are also likely to be lengthened. QRS widening provides a valuable clue to overdose in the unconscious patient who has ingested an unknown drug. Sinus tachycardia, conduction disturbances (especially right bundle branch block), and ventricular arrhythmias may persist long after serum levels normalize because of avid tissue binding. Return of the QRS width to baseline is an indication that the risk of significant arrhythmias and seizures has decreased. (Observation for 12 hours after the QRS normalizes is a reported practice.)

Management includes securing the airway and stabilizing vital signs. ECG monitoring should be continued and gastric lavage considered if the patient presents within 1 hour of ingestion. Activated charcoal may also be considered in this early stage post ingestion. It is advisable to alkalize the blood and to load with sodium bicarbonate boluses to pH of 7.5 to 7.55 for prolonged QRS or wide-complex arrhythmias. If alkalization is effective, an infusion is maintained for 4 to 6 hours and then tapered. Hypertonic saline or 20% lipid emulsion is often given for refractory cases, and magnesium is administered for torsades de pointes. Benzodiazepines may be used for seizures. Norepinephrine or phentolamine, direct alpha agonists, may be administered for refractory hypotension.

Sodium bicarbonate un couples the cyclic antidepressant from the myocardial sodium channels, and alkalization with bicarbonate may be superior to hyperventilation. Hypertonic saline solution has been reported to be effective in some patients with refractory cardio toxicity. Bicarbonate may also benefit hypotension associated with myocardial depression that is unresponsive to other interventions. In seizing patients with unstable hemodynamic or respiratory status, it may be necessary to use a muscle relaxant to establish an airway and effective circulation before cerebral discharges are controlled. Where neuromuscular blockade is employed, continuous EEG monitoring is required. Because of high lipid solubility and protein binding, neither hemodialysis nor hemoperfusion is generally recommended for drug removal.

Serotonin Reuptake Inhibitors

A variety of psychoactive medications act by increasing brain serotonin concentrations. Because of their effectiveness and low toxicity, SSRIs (e.g., sertraline, paroxetine, fluoxetine, citalopram, trazodone) have largely supplanted cyclic antidepressants. In addition to the reuptake inhibitors, serotonin levels can be augmented by drugs that are serotonin agonists (e.g., buspirone, lithium, metoclopramide) and those that increase serotonin synthesis (e.g., L-tryptophan) or release (e.g., amphetamines, cocaine, ecstasy) or inhibit its breakdown (monoamine oxidase inhibitors, including linezolid). Toxic levels of serotonin can result from an isolated large ingestion of a single SSRI but more often are the result of simultaneous ingestion of several drugs from different classes or the addition of an MAO inhibitor to chronic SSRI therapy. This risk is magnified because many current SSRIs have very long half-lives. When toxicity follows a discrete large ingestion, symptoms are seen within minutes to hours and resolve within 48 hours.

Diagnosis is made by history and an appropriate therapeutic presentation because drug levels are not clinically available. The most common manifestations of serotonin excess (the “serotonin syndrome”) are fever, confusion, restlessness, mydriasis, hyperreflexia, shivering, and nausea. In severe cases, seizures, coma, myoclonus, muscle rigidity, and rhabdomyolysis are seen. Because of the presence of fever and neuromuscular findings, serotonin syndrome can be confused with neuroleptic malignant syndrome (NMS); however, NMS victims have normal pupil sizes, have cogwheeling and lead-pipe rigidity, and have been exposed to a neuroleptic agent. Treatment is largely supportive and includes withholding all drugs with serotonin-enhancing properties, sedation, anticonvulsants, mechanical ventilation, and external cooling. The 5-HT2A antagonist cyproheptadine (12 to 32 mg/24 h) has been reported to be effective, but there is little controlled experience with its use. Dialysis and hemoperfusion are not effective. Benzodiazepines are effective in treatment of the agitation, muscle rigidity, and seizures. Most cases of serotonin syndrome resolve in 24 to 72 hours.

Calcium Channel Blocking and β-Blocking Drugs

In sufficient doses, β-blocking and calcium channel blocking drugs are highly lethal cardiovascular poisons. As competitive antagonists for β-adrenergic receptors, the toxicity of different β-blockers varies depending on receptor selectivity (β1 receptors in the heart vs. β2 receptors in airways and peripheral vessels). Although the mechanism is different (blocking calcium transit through cell membranes), calcium channel antagonists result in similar impairments of cardiac and vascular function. Bradycardia and hypotension (resulting from a combination of decreased myocardial contractility and peripheral vasodilation) are the major toxic manifestations of both classes. The importance of each mechanism varies somewhat by drug. For example, β-blockers with membrane-stabilizing properties (e.g., propranolol, acetylbutol, betaxolol, pindolol) are likely to cause conduction defects (QRS widening) and impaired contractility, whereas nonselective β-blockers may cause bronchospasm. Likewise, manifestations of calcium channel blocker overdose vary by drug. For example, verapamil and diltiazem have comparable deleterious effects on sinus node and AV node activity, but...
dittiazem has less effect on contractility than verapamil. By contrast, nifedipine and amiodipine have less impact on conduction and contractility but much greater peripheral vasodilating effects. Although β-blockers have been associated with hypoglycemia, suppression of insulin secretion that occurs with calcium channel blocker use often leads to hyperglycemia. Except for patients with severe preexisting asthma, bronchospasm following β-blocker overdose is rarely clinically significant, and when it occurs, it is easily treated with inhaled β-adrenergic agonists. Both classes of drugs are rapidly absorbed; thus, when harmful quantities of short-acting agents are ingested, manifestations are likely within 6 hours. However, when a sustained-release preparation is taken, toxicity may not be evident for 12 hours, and when adverse effects are seen, they last a long time. As a corollary, patients without cardiovascular manifestations 12 or more hours after reported ingestion are unlikely to develop serious toxicity. Initial treatment can include gastric lavage if patients present soon after ingestion. If a sustained-release preparation has been ingested, whole bowel irrigation may be considered. Treatment of both classes of overdose should focus on cardiovascular support. Fluids will correct the hypotension resulting from reduced preload and are often effective for hypotension induced by the vasodilating calcium channel blockers. By contrast, fluid is not a useful treatment for bradycardia or impaired contractility. For symptomatic bradycardia, atropine, isoproterenol, or epinephrine can be tried as cardiac accelerants, but pacing may be required. Unfortunately, in this setting, it is often difficult to achieve pacing capture by either transcutaneous or intravenous routes. When both bradycardia and systemic vasodilation occur, use of a combined α- and β-agonist such as norepinephrine may be helpful. Repeated doses of calcium chloride (1 g IV) have been recommended as treatment for β-blocker or calcium channel blocker overdose with hemodynamic abnormalities. Glucagon (2 to 5 mg IV over 1 minute) followed by an infusion of 1 to 10 mg/h has been advocated for both classes of overdose because it increases cAMP and in turn calcium influx. Glucagon may not completely correct hypotension or bradycardia; thus, administration of norepinephrine or epinephrine should also be considered. Euglycemic administration of very high doses of insulin (from 0.5 to up to 10 units/kg/h) also results in rapid correction of the bradycardia, the myocardial depression, and the hypotension resulting from both classes of drug overdose. Although solid experimental data and convincing case series support the use of high-dose insulin in the treatment of beta blocker overdose, calcium channel overdose, and selected other drugs that impair myocardial contractility, most institutions have relatively limited experience with this useful and potentially lifesaving measure. The exact mechanism of action has been observed to occur in higher doses of insulin that can stimulate the conversion of glucose to lactate, which can then be metabolized in the liver. This will help to increase blood glucose levels and return the patient's circulation to normal. As such, it is often less expensive, safer, and easier to administer than glucagon. However, glucagon may not completely correct hypotension or bradycardia; thus, administration of norepinephrine or epinephrine should also be considered.

Miscellaneous Agents

Toxic Plants

Toxic plant ingestions are common but fatalities are rare. Although all parts of the plant may be poisonous, roots or seeds may contain higher concentrations of toxins. A variety of plants contain anticholinergic alkaloids such as hyoscymamine and atropine. These plants include Jimsonweed, angel's trumpet, deadly nightshade, mandrake, and black henbane. Anticholinergic symptoms typically begin within 1 hour of ingestion and may continue for days. Severe toxicity results in agitation, hallucinations, hyperthermia, tachycardia, rhabdomyolysis, renal failure, and death. Without aggressive supportive care, death can result from rhabdomyolysis-induced renal failure, disseminated intravascular coagulation, cardiac rhythm changes, or seizures. Sedation with benzodiazepines may be required to control symptoms. In the absence of contraindications such as a history of seizures or the presence of cardiac conduction delay, phystostigmine is a treatment option. Duration of anticholinergic effects can outlast the effects of physostigmine, making redosing necessary.

Indole compounds capable of producing hallucinations are found in morning glory and Hawaiian baby wood rose. Nutmeg and peyote contain compounds which structurally resemble amphetamines yet also interact with serotonin receptors. Illness begins with vomiting followed by hallucinations. Mydriasis is common along with agitation, tachycardia, and rhabdomyolysis. Agitation is best treated with benzodiazepines. Differential diagnosis for poisoning by these plants includes poisoning by anticholinergic botanicals. Marijuana is probably the best known of these hallucinogens. Poisoning frequently occurs following the misidentification of toxic mushrooms as edible species. Such consequential errors account annually for numerous fatalities worldwide. In general, if the onset of gastrointestinal symptoms occurs greater than 6 hours after ingestion of mushrooms, concern for ingestion of hepatotoxic or neurotoxic mushrooms increases. Early vomiting makes systemic toxicity less likely with the exception of anillic norleucine-containing mushrooms. Ingestion of more than one type of mushroom makes the above rule unreliable.

Consumption of toxic mushrooms can lead to multiple organ insults. Among changes seen are hepatic and renal failure, encephalopathy, seizures, coma, hemolysis, hallucinations, hemolytic anemia, and rhabdomyolysis. Renal insufficiency is managed with dialysis and other renal replacement therapies. Atropine is given for muscularic symptoms. Pyridoxine has been given for seizures and methylene blue for methemoglobinemia. In most cases, however, supportive care of affected organ systems remains the foundation of appropriate intervention.

Lithium

Lithium, historically used to treat bipolar disorders, has gained popularity for therapy of a variety of psychiatric conditions. When overdosed, lithium presents a unique problem because of its largely intracellular distribution and narrow therapeutic margin. Even small incremental ingestions can produce toxicity among patients on chronic stable therapy. Lithium has a long half-life and is filtered by the kidney, so toxicity can also result from any condition that reduces the glomerular filtration rate. While mild intoxication causes fine tremor and perhaps confusion, severe toxicity is associated with major movement disorders such as clonus, fasciculations, choreoathetosis, opisthotonos, and seizures. Patients who chronically ingest lithium are more predisposed to toxic effects. A serum lithium level should be evaluated at presentation and 2 hours later to evaluate the possibility of increasing concentration. Serum lithium levels greater than 2.5 to 4 mmol/L may indicate life-threatening toxicity. Clinical findings must be combined with this laboratory data.

Whole bowel irrigation may be considered in serious toxicity because lithium is not absorbed by charcoal. Volume resuscitation should be aimed at restoring adequate urine output, but forced diuresis is not effective in facilitating lithium excretion. Diuretics may worsen toxicity and should be avoided. Hemodialysis is indicated for such lifethreatening toxicity manifestations as renal and/or neurological impairment, which are associated with drug levels exceeding 4 mmol/L in acute ingestion or 2.5 mmol/L in chronic ingestion. The lithium level, duration of exposure, and severity of clinical symptoms should be balanced against risks of hemodialysis. Because of redistribution between intracellular and extracellular compartments, a rebound increase in lithium level may occur 6 to 8 hours after completion of the dialysis run. Continuous venovenous hemodiafiltration has been used to remove lithium and may be associated with a less dramatic rebound. Sodium polystyrene sulfonate has been suggested to decrease lithium absorption, but evidence of clinical benefit is lacking and complications of hypokalemia, hypervolemia, and fluid overload may result.

Lithium

Lithium, historically used to treat bipolar disorders, has gained popularity for therapy of a variety of psychiatric conditions. When overdosed, lithium presents a unique problem because of its largely intracellular distribution and narrow therapeutic margin. Even small incremental ingestions can produce toxicity among patients on chronic stable therapy. Lithium has a long half-life and is filtered by the kidney, so toxicity can also result from any condition that reduces the glomerular filtration rate. While mild intoxication causes fine tremor and perhaps confusion, severe toxicity is associated with major movement disorders such as clonus, fasciculations, choreoathetosis, opisthotonos, and seizures. Patients who chronically ingest lithium are more predisposed to toxic effects. A serum lithium level should be evaluated at presentation and 2 hours later to evaluate the possibility of increasing concentration. Serum lithium levels greater than 2.5 to 4 mmol/L may indicate life-threatening toxicity. Clinical findings must be combined with this laboratory data.

Whole bowel irrigation may be considered in serious toxicity because lithium is not absorbed by charcoal. Volume resuscitation should be aimed at restoring adequate urine output, but forced diuresis is not effective in facilitating lithium excretion. Diuretics may worsen toxicity and should be avoided. Hemodialysis is indicated for such lifethreatening toxicity manifestations as renal and/or neurological impairment, which are associated with drug levels exceeding 4 mmol/L in acute ingestion or 2.5 mmol/L in chronic ingestion. The lithium level, duration of exposure, and severity of clinical symptoms should be balanced against risks of hemodialysis. Because of redistribution between intracellular and extracellular compartments, a rebound increase in lithium level may occur 6 to 8 hours after completion of the dialysis run. Continuous venovenous hemodiafiltration has been used to remove lithium and may be associated with a less dramatic rebound. Sodium polystyrene sulfonate has been suggested to decrease lithium absorption, but evidence of clinical benefit is lacking and complications of hypokalemia, hypervolemia, and fluid overload may result.

Misellaneous Agents

Toxic Plants

Toxic plant ingestions are common but fatalities are rare. Although all parts of the plant may be poisonous, roots or seeds may contain higher concentrations of toxins. A variety of plants contain anticholinergic alkaloids such as hyoscymamine and atropine. These plants include Jimsonweed, angel's trumpet, deadly nightshade, mandrake, and black henbane. Anticholinergic symptoms typically begin within 1 hour of ingestion and may continue for days. Severe toxicity results in agitation, hallucinations, hyperthermia, tachycardia, rhabdomyolysis, renal failure, and death. Without aggressive supportive care, death can result from rhabdomyolysis-induced renal failure, disseminated intravascular coagulation, cardiac rhythm changes, or seizures. Sedation with benzodiazepines may be required to control symptoms. In the absence of contraindications such as a history of seizures or the presence of cardiac conduction delay, phystostigmine is a treatment option. Duration of anticholinergic effects can outlast the effects of physostigmine, making redosing necessary.

Indole compounds capable of producing hallucinations are found in morning glory and Hawaiian baby wood rose. Nutmeg and peyote contain compounds which structurally resemble amphetamines yet also interact with serotonin receptors. Illness begins with vomiting followed by hallucinations. Mydriasis is common along with agitation, tachycardia, and rhabdomyolysis. Agitation is best treated with benzodiazepines. Differential diagnosis for poisoning by these plants includes poisoning by anticholinergic botanicals. Marijuana is probably the best known of these hallucinogens. Poisoning frequently occurs following the misidentification of toxic mushrooms as edible species. Such consequential errors account annually for numerous fatalities worldwide. In general, if the onset of gastrointestinal symptoms occurs greater than 6 hours after ingestion of mushrooms, concern for ingestion of hepatotoxic or neurotoxic mushrooms increases. Early vomiting makes systemic toxicity less likely with the exception of anillic norleucine-containing mushrooms. Ingestion of more than one type of mushroom makes the above rule unreliable.

Consumption of toxic mushrooms can lead to multiple organ insults. Among changes seen are hepatic and renal failure, encephalopathy, seizures, coma, hemolysis, hallucinations, hemolytic anemia, and rhabdomyolysis. Renal insufficiency is managed with dialysis and other renal replacement therapies. Atropine is given for muscularic symptoms. Pyridoxine has been given for seizures and methylene blue for methemoglobinemia. In most cases, however, supportive care of affected organ systems remains the foundation of appropriate intervention.

Lead

Overall prevalence of lead toxicity is declining but this condition remains an important health concern worldwide. Most cases of lead toxicity result from chronic exposure rather than a single acute ingestion. Acute ingestion, although rare, results in diarrhea, hemolysis, hepatic necrosis, encephalopathy, and renal failure.
More commonly, patients present with acute signs and symptoms from previously unrecognized chronic lead poisoning. Ingestion of elemental lead objects such as curtain weights may cause delayed life-threatening poisoning. Chronic poisoning produces anemia, abdominal pain, malaise, renal failure, and encephalopathy. In children, radiographs reveal “lead lines” in bones, which represent areas of increased calcium density rather than lead deposition. Retained bullets do not produce lead poisoning unless fragments are in prolonged contact with synovial fluid, pleural fluid, or CSF.

When evaluating patients for lead toxicity, only whole blood lead concentrations should be used when deciding on management strategy. Free erythrocytic protoporphyrin and zinc protoporphyrin concentrations may also be helpful. Chronic toxicity will have elevated protoporphyrin levels, whereas acute toxicity will not show acute elevation in protoporphyrin levels.

Appropriate therapy involves interpreting the patient's whole blood lead concentration in context with age and clinical symptoms. Asymptomatic patients with moderately elevated lead concentrations typically do not require chelation therapy. If chelation therapy is recommended for lead exposure, 2,3-mesodimercaptosuccinic acid or dimercaprol and calcium disodium ethylenediaminetetraacetic acid may be used.

In addition to supportive care including benzodiazepines or barbiturates for convulsions and treatment of intracranial hypertension, chelation therapy is usually begun with dimercaprol 75 mg/m², deep IM injection every 4 hours for 5 days. At least 4 hours following administration of dimercaprol, calcium disodium ethylenediaminetetraacetic acid 1,500 mg/m² IV per day (continuous infusion or 2 to 4 divided doses) should be initiated and continued for at least 5 days. Nephrotoxicity may complicate the use of chelating agents.

**SUGGESTED READINGS**


Chapter 34
Neurologic Emergencies

• Key Points

1. Many critical care interventions such as endotracheal intubation, invasive mechanical ventilation, bodily restraint, sleep deprivation, protracted sedation, and painful bedside procedures promote the delirium so often seen in the intensive care unit. Drug effects, severe sepsis, and hepatic and renal failure are prominent causes of metabolic encephalopathy.

2. Patients with altered mental status should have the airway assured and ventilation and perfusion restored so that the brain receives adequate quantities of glucose-replete and well-oxygenated blood. Only after this initial stabilization should further evaluation be undertaken.

3. Seizure activity should be terminated as quickly as possible, usually by administering an intravenous benzodiazepine followed by phenytoin while simultaneously assessing potential structural or metabolic precipitants of the seizure. Many of the seizures that occur in the ICU are nonconvulsive.

4. When stroke is suspected on clinical grounds, an urgent noncontrast CT guides treatment. Tissue plasminogen activator and other endovascular therapies offer benefit in ischemic stroke if administered within several hours of the event. Conversely, correction of coagulation disorders is essential for managing hemorrhagic stroke.

5. Cerebral perfusion pressures less than 60 mm Hg should be avoided. In head injury, raising mean arterial pressure and lowering intracranial pressure help maintain perfusion of jeopardized but viable brain tissue. Hyperventilation works only transiently. Osmotic agents provide more durable benefit.

6. In trauma victims with potential head or spine injury, airway patency, ventilation, oxygenation, and effective circulation are primary considerations. While achieving these goals, special attention should be paid to immobilization of the cervical spine or other spine levels at risk.

7. After initial stabilization, a thorough neurologic examination and radiographs of the spine and head should be obtained to evaluate trauma patients for the possibility of a surgically correctable lesion. CT is the preferred imaging modality.

8. After stabilization of the neurologically impaired patient, usually mundane medical problems including ileus, gastric stress ulceration, urinary tract infection, aspiration, atelectasis, deep venous thrombosis, and decubitus ulcers present the large challenges. Appropriate prophylactic measures should be instituted for each of these conditions as soon as possible.

9. Brain death is a state of irreversible absence of function at all levels of the brain (cortex, midbrain, and brainstem). Clinically, this is manifest as an absence of arousal, absence of midbrain reflexes (predominately cranial nerve signs), and absence of spontaneous breathing despite significant hypercapnia. The diagnosis generally cannot be made in the presence of ongoing hypothermia or drug intoxication.

Alterations of consciousness and cognition are both significant daily problems in the intensive care unit (ICU). It is not shocking that depressed consciousness has profound prognostic importance, but many clinicians are surprised to learn that development of confusion or delirium also has powerful predictive value.
DELIRIUM

Delirium is defined by the National Institutes of Health as a sudden, severe confusion and rapid change in brain function that may occur with physical or mental illness. The most common feature of delirium, thought by many to be its cardinal sign, is inattention. Delirium is a nonspecific but generally reversible manifestation of acute illness that appears to have many causes including sleep deprivation and inappropriate type and level of sedation. Painful bedside procedures, endotracheal intubation, and prolonged mechanical ventilation have also been associated with its development. The most frequent conditions associated with delirium are shown in Figure 34-1.

The pathophysiology of delirium occurring during critical illness is incompletely characterized. Increased risk has been attributed to the use of GABA agonist and anticholinergic drugs, leading to the suggestion that GABAergic and cholinergic neurotransmitter systems are integrally involved. Central cholinergic deficiency may be a final common pathway. Other hypotheses include excess dopaminergic activity and direct neurotoxic effect of inflammatory cytokines. All of these hypotheses are unproven, which complicates pharmacologic management.

Studies using MRI have shown a positive association between the duration of delirium in the ICU and both cerebral atrophy and cerebral white matter disruption. These investigations indicate that either delirium in the ICU gives rise to alteration in brain structure or that the presence of cerebral atrophy and white matter disruption renders patients more susceptible to delirium.

![Figure 34-1](image)

**FIGURE 34-1. Relative frequency of (nonsedative) causes of delirium in nontrauma ICU patients.**

Sepsis, hepatic failure, and renal failure rank as the most common causes.

Regardless of cause, and underlying pathophysiology, delirium is a common and serious event in the critically ill. Because there is no diagnostic blood, EEG, or imaging test for delirium, it remains a clinical diagnosis. Incidence
estimates for delirium in the critical care unit range from 16% to 89% with the reported incidence affected both by the characteristics of the population studied and diagnostic criteria employed. Risk factors identified include advanced age and the presence of conditions associated with coma followed by treatment with sedative medications, a neurologic diagnosis, and increasing severity of overall illness. Although causality is yet to be shown, the diagnosis of delirium is associated with increased mortality (estimated as a 10% increase in relative risk of death for each day of delirium) as well as with decreased long-term cognitive function.

Two distinct forms of delirium have been identified: hypoactive and agitated (or hyperactive). When individual patients intermittently have both forms, mixed delirium is identified. The more common hypoactive form is characterized by inattention, disordered thinking, and decreased level of consciousness without agitation. Agitated delirium is more dramatic but much less common among patients with delirium in the ICU. Patients with hypoactive delirium are less likely to survive, but those who do survive may have better long-term function than those with agitated or mixed delirium.

In routine practice, ICU staff members frequently do not diagnose delirium. In fact, almost three quarters of patients having the condition may elude diagnosis by their caregivers. Two clinical scales are in routine use for characterizing delirium: the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC). The CAM-ICU reports a dichotomous assessment at one time point, whereas the ICDSC lists signs that can be observed over an extended period. Although use of these scales is helpful in diagnosing delirium, it is not clear that use of these scales is more sensitive than assessments made by a trained bedside staff that are prompted to look for delirium.

There is some evidence that delirium may be preventable. Repeated reorientation, noise reduction, cognitive stimulation, vision and hearing aids, adequate hydration, and early mobilization may reduce the incidence of delirium in hospitalized patients. Among critical care patients, the duration of delirium was reduced with early mobilization during interruptions of sedation. Reduced and optimized use of sedating agents may also help. Sedation with dexmedetomidine rather than benzodiazepines may reduce the incidence of delirium in the ICU.

There is little evidence to guide management of established delirium. Agents that have been associated with improved outcome in the available trials include quetiapine, olanzapine, haloperidol, and dexmedetomidine.

**COMA**

Coma is characterized by the absence of arousal (wakefulness, vigilance) and of awareness of self and environment lasting for more than 1 hour. Comatose patients have closed eyes, do not speak, and do not arouse to verbal, tactile, or noxious stimuli. Some causes of coma are readily identified, whereas others require extensive testing to discover the etiology. Diagnostic and therapeutic steps should occur simultaneously. The Emergency Neurological Life Support group has proposed a protocol and checklist for initial management of the patient with coma (Fig. 34-2). Etiologies of coma are reviewed in Table 34-1.
Pathophysiology

Consciousness has two components: arousal and awareness. Failure of arousal results from reticular activating system (RAS) or diffuse bilateral hemispheric dysfunction. Continuous stimulation by the RAS is required for the appearance of wakefulness. Conversely, awareness (a cognitive function) requires coordinated function of both cerebral cortices. Arousal may occur without awareness, but not the converse. From its origin in the midpons, the RAS radiates diffusely outward to the cerebral cortex. It is this protected origin and wide distribution that prevents coma, unless a diffuse process (e.g., drug or metabolic toxin) simultaneously impairs both sides of the cerebral cortex or the RAS is interrupted near its pontine root. Although this simple schema generally explains arousal and awareness, the dominant cortical hemisphere plays a disproportionate role in maintaining consciousness, and selective damage to both
Frontal lobes can also result in coma.

**Table 34-1. Etiologies of Coma**

<table>
<thead>
<tr>
<th>Neurologic</th>
<th>Toxic-Metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td></td>
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<tr>
<td></td>
<td>Subdural hematoma</td>
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<tr>
<td></td>
<td>Epidural hematoma</td>
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<tr>
<td></td>
<td>Parenchymal hemorrhages</td>
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<tr>
<td></td>
<td>Diffuse axonal injury</td>
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<tr>
<td>Cardiovascular</td>
<td></td>
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<tr>
<td></td>
<td>Intracerebral hemorrhage</td>
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<tr>
<td></td>
<td>Subarachnoid hemorrhage</td>
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<tr>
<td></td>
<td>Ischemic stroke</td>
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<tr>
<td></td>
<td>Anoxic-ischemic encephalopathy</td>
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<tr>
<td>CNS Infections</td>
<td></td>
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<tr>
<td></td>
<td>Meningitis</td>
</tr>
<tr>
<td></td>
<td>Encephalitis</td>
</tr>
<tr>
<td></td>
<td>Abscess</td>
</tr>
<tr>
<td>Neuroinflammatory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disorders</td>
</tr>
<tr>
<td></td>
<td>Acute disseminated encephalomyelitis</td>
</tr>
<tr>
<td></td>
<td>Autoimmune encephalitis</td>
</tr>
<tr>
<td>Neoplasms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metastatic</td>
</tr>
<tr>
<td></td>
<td>Primary CNS</td>
</tr>
<tr>
<td></td>
<td>Carcinomatous meningitis</td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonconvulsive status epilepticus</td>
</tr>
<tr>
<td></td>
<td>Postictal state</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posterior reversible encephalopathy syndrome</td>
</tr>
</tbody>
</table>
Osmotic demyelination syndrome

Metabolic Encephalopathies

Hypoglycemia
Hypoglycemia
Diabetic ketoacidosis; hyperosmolar nonketotic hyperglycemia
Hepatic encephalopathy
Uremia
Hyponatremia
Hypernatremia
Myxedema
Adrenal failure
Hypercalcemia
Wernicke disease
Sepsis

Drug/Medication Overdose Drugs of abuse (opiod, alcohol, methanol, ethylene glycol, amphetamines, cocaine)

Sedative-hypnotics
Narcotics
Aspirin
Acetaminophen
SSRI
Tricyclic antidepressants
Antipsychotics
Carbon monoxide
Anticonvulsants

Environmental Causes

Heat stroke
Hypothermia
Carbon monoxide


Coma may arise from a wide variety of diffuse or focal conditions affecting the central nervous system (CNS); however, all coma results from four basic pathophysiologic mechanisms: (1) metabolic or toxic encephalopathy, (2) generalized seizures, (3) compression of the midbrain or cerebral cortices by structural lesions or increased intracranial pressure (ICP), and (4) inadequate cerebral perfusion. The extent of neurologic impairment resulting from any potential cause of coma is modified by the patient's age and underlying neurologic and vascular status. Metabolic insults that do not change cognition in a healthy young person can result in profound coma in an elderly patient with impaired circulation.
Etiology

**Metabolic Disorders**

Apart from structural neurosurgical insults (e.g., head trauma, subarachnoid hemorrhage [SAH], massive stroke, brain tumor), metabolic encephalopathy is the most common cause of coma. A comparison of the usual clinical features of structural and metabolic coma is presented in Table 34-2. Because metabolic encephalopathy affects the cortex and brainstem diffusely, abrupt focal deficits and progressive rostrocaudal losses seen with supratentorial mass lesions do not usually occur. Rather, patients exhibit slowly evolving symmetric deficits, often preceded by somnolence or confusion. A variety of common disorders, including drug overdose, hypoxia, hypotension, hypoglycemia, dehydration, sepsis, hepatic encephalopathy, and uremia, can all contribute to impaired consciousness. The common reversible causes of coma are summarized in Table 34-3.

It is difficult to provide absolute guidelines as to the magnitude of a single abnormality necessary to cause coma because multiple derangements often coexist. Age, presence of underlying diseases, and the rapidity of development also determine impact on consciousness. Yet, as a general rule, when acting alone, it is uncommon for glucose greater than 50 or less than 500 mg/dL, Na⁺ greater than 120 or less than 155 mEq/L, Ca²⁺ less than 12 mg/dL, or Mg²⁺ greater than 0.8 or less than 10 mg/dL to produce coma. Only very rarely do disorders of other electrolytes alter consciousness. The precise cause of unconsciousness in patients with renal failure is unknown; however, uremia alone rarely causes coma until the blood urea nitrogen (BUN) exceeds 100 mg/dL. (Renal insufficiency probably alters consciousness through multiple mechanisms, including metabolic acidosis, electrolyte abnormalities, accumulation of metabolic toxins or drugs, and increased permeability of the blood-brain barrier.) Similarly, the exact cause of coma in patients with liver failure is unknown, but accumulation of endogenous (e.g., glutamine) and exogenous toxins (e.g., drug metabolites) and cerebral edema all play some role in the process (see Chapter 31). Cerebral edema is a greater problem in the setting of acute hepatic failure. There is such an imprecise and inconsistent correlation between serum ammonia levels and mental status that no rule defines the level of ammonia associated with coma.

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**Table 34-2. Clinical Characteristics of Causes of Coma**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Traumatic or Vascular</th>
<th>Toxic or Metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td>Injury</td>
<td>Toxin, drug exposure history</td>
</tr>
<tr>
<td></td>
<td>Uncontrolled hypertension</td>
<td>History of liver or kidney failure, COPD, or diabetes</td>
</tr>
<tr>
<td></td>
<td>Seizure</td>
<td>Recent hypoxic event</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Abrupt</td>
<td>Gradual</td>
</tr>
<tr>
<td><strong>Rate of progression</strong></td>
<td>Rapid (minutes) deterioration</td>
<td>Slower (hours) progression common</td>
</tr>
</tbody>
</table>
Pattern of progression
May be stuttering or gradual
Rostrocaudal loss of function
Global impairment from the start No rostrocaudal pattern

Focality
Focal lesions common
Focal lesions rare

Table 34-3. Common Reversible Causes of Altered Mental Status

<table>
<thead>
<tr>
<th>Medical Conditions</th>
<th>Surgery and Trauma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoperfusion</td>
<td>Drug overdose</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>Carbon monoxide</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Wernicke encephalopathy</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>Temperature disorders</td>
</tr>
<tr>
<td>Myxedema</td>
<td>CNS hemorrhage</td>
</tr>
<tr>
<td>Hypertension</td>
<td>CNS infections (e.g., brain abscess,</td>
</tr>
<tr>
<td></td>
<td>meningitis, encephalitis)</td>
</tr>
</tbody>
</table>

More firm guidelines can be offered with respect to the impact of hypoxemia and hypercapnia on consciousness. Tolerance of hypoxemia depends not only on the extent of desaturation but also on whether gradual adaptation has occurred and the extent to which compensatory mechanisms are available. The major mechanisms of acute compensation are increased cardiac output, increased \( O_2 \) extraction, anaerobic metabolism, and improved unloading of \( O_2 \) resulting from tissue acidosis. Most individuals without cardiac disease or anemia who are acutely hypoxemic remain asymptomatic until \( PaO_2 \) falls below 50 mm Hg. At that level, malaise, light-headedness, nausea, vertigo, impaired judgment, and reduced coordination are noted. Confusion develops as \( PaO_2 \) falls into the 35- to 50-mm Hg range. As \( PaO_2 \) declines below 35 mm Hg, urine output slows, bradycardia and conduction system blockade develop, lactic acidosis appears, and the patient becomes lethargic or obtunded. At levels near 25 mm Hg, the unadapted normal individual loses consciousness, and minute ventilation falls because of respiratory center depression. As for all other metabolic toxins, the effects of carbon dioxide (\( CO_2 \)) depend not only on the absolute level of \( CO_2 \) but also on its rate of accumulation. A \( PaCO_2 \) less than 60 mm Hg seldom impairs consciousness, but as levels rise above this threshold, headache and lethargy are commonly observed. Asterixis and myoclonus occur as levels mount even higher, but surprisingly massive elevations in
CO₂ (often double or triple normal values) are usually necessary to render a patient unconscious.

Generally, a cerebral perfusion pressure (CPP) (mean arterial pressure [MAP]-ICP) must exceed 50 mm Hg to perfuse the brain adequately; however, otherwise young healthy patients may maintain consciousness despite severe reductions in MAP. By contrast, patients with chronic hypertension, cerebrovascular disease, or elevated ICP may remain underperfused despite much higher CPP levels.

Severe sepsis frequently alters consciousness; however, mental status changes usually fall short of true coma. The mechanisms are multifactorial. Obviously, direct infection of the CNS can render a patient unconscious. In addition, severe sepsis is usually associated with some degree of hypoxemia, and almost 75% of septic patients will develop hypotension—both factors which contribute to mental status changes. Inflammatory cytokines may directly impair consciousness. Sepsis-induced coma is particularly common in the febrile elderly patient, where altered mental status often poses difficult management decisions. Frequently deliberated diagnoses are severe sepsis alone, or sepsis complicated by dehydration, electrolyte abnormalities, meningitis, and intracranial structural lesions, such as a brain abscess or hemorrhage. Timely antibiotic therapy is desirable for all treatable infections, but confirming the diagnosis and nailing down a specific organism so as to best choose antimicrobial therapy usually requires a lumbar puncture (LP). Unfortunately, LP incurs some risk in the presence of coagulopathy, anticoagulation, or history of trauma, an LP is almost certainly safe and can be performed before or without a head CT scan. (Not that long ago, the decision to perform an LP was always made only based upon history and examination.) If head trauma, papilledema, new-onset seizures, or focal neurologic deficit complicates the evaluation of a potentially infected patient, probably the best course is to obtain blood cultures, administer empiric antibiotics, and proceed to the CT scanner before LP. In any case, if logistical limitations preclude prompt CT scanning and intracranial infection is a real possibility, it is best to begin antibiotic treatment, even if doing so impedes making a definitive microbiological diagnosis.

Medication ingestion and toxin exposure are the most frequent causes of nontraumatic coma. Opiates, benzodiazepines, ethanol, and antidepressants are the most common drug classes implicated. Chemical-induced mental status changes are typically multifactorial; commonly, several consciousness-depressing drugs are simultaneously ingested, and the drugs or toxins often lead to changes in oxygenation or perfusion that contribute to coma. For example, narcotic overdose is often combined with ingestions of benzodiazepine and/or alcohol. Although direct effects of these drugs alone can cause coma, they can also impair consciousness by producing hypoventilation or hypotension (see Chapter 33).

Seizures

Generalized seizures may induce unconsciousness during the ictal phase or as a postictal phenomenon. Distinguishing a seizure from other causes of coma is easy if convulsive activity is observed or consciousness returns rapidly after a suspected seizure in an otherwise healthy patient. However, in the ICU, many seizures do not cause visible convulsions. In addition, a patient with metabolic encephalopathy, prolonged seizures (status epilepticus), or prior stroke may suffer a long postictal period. Status epilepticus often arises from an underlying structural or metabolic cause. Thus, delayed return of consciousness following a seizure should prompt consideration of a structural lesion (e.g., tumor, stroke, SAH, subdural hematoma) or underlying metabolic disorder (e.g., hypoglycemia, toxin ingestion, or electrolyte disturbance). As with metabolic encephalopathy, seizures that cause loss of consciousness generally tend to produce symmetric neurologic defects unless there is an underlying structural abnormality. In contrast to metabolic encephalopathy, the loss of consciousness associated with
seizures is usually instantaneous rather than gradual. If concern for seizures is high, it is appropriate to initiate therapy before confirming the diagnosis.

**Structural Lesions**

Although supratentorial mass lesions are generally confined to one hemisphere, they cause coma by increasing ICP or by impairing RAS function through pressure on the brainstem. Unless located exactly in the midline, supratentorial mass lesions usually produce hemispheric (unilateral) findings that precede loss of consciousness. Because cerebral function is progressively lost in a rostrocaudal manner, there is a relatively predictable progression. If unchecked, the process culminates in central or uncal herniation. In central herniation, the midbrain is pressed directly into the foramen magnum. Clinical manifestations include miosis, decerebrate posturing, and lateral gaze palsy as the sixth cranial (abducens) nerve is stretched. Uncal herniation occurs as asymmetric pressure forces the medial portion of the temporal lobe to cross the tentorium, compressing the midbrain. Clinical manifestations include a fixed dilated pupil, third cranial (oculomotor) nerve palsy, and hemiparesis. By contrast, when infratentorial lesions (e.g., brainstem strokes, cerebellar hemorrhage) cause coma, very rapid loss of consciousness without rostrocaudal progression is typical.

**Approach to the Comatose Patient**

**History**

Because their pathophysiology and treatments differ radically, metabolic and structural causes of coma must be distinguished as quickly as possible. The history is helpful in making this separation if it reveals trauma or drug ingestion. Sudden onset of coma suggests a seizure or a vascular event (e.g., SAH, brainstem stroke). The onset of coma after minutes to hours of a focal deficit suggests supratentorial intracerebral hemorrhage with progressively increasing ICP. A slowly evolving focal deficit occurring over days to weeks before loss of consciousness suggests abscess, tumor, or subdural hematoma, whereas progression to coma over minutes to hours without a focal deficit favors a metabolic cause.

The setting in which coma develops may suggest trauma, hyperthermia, hypothermia, or toxic exposure (e.g., organophosphates, carbon monoxide). Medications found near the comatose patient are particularly helpful. For example, not only may the offending compound(s) be discovered, but medication containers bearing the name of the prescribing physician may allow further history to be obtained. At the very least, knowledge of a patient's medications suggests underlying diseases. In patients with alcoholism, intoxication with ethanol, ethylene glycol, methanol, or isopropyl alcohol should be suspected. For patients with diabetes, hypoglycemia, diabetic ketoacidosis (DKA), and hyperosmolarity are common causes of coma. Underlying medical problems such as hypothyroidism, renal failure, cirrhosis, or psychiatric illness also increase the likelihood of a metabolic etiology, whereas a history of falling, previous stroke, brain tumor, extracranial neoplasm, or atrial fibrillation favors structural or vascular problems. Patients known to have malignant tumors are subject to both structural lesions of the brain (e.g., metastases and hemorrhage) and metabolic causes (e.g., hyponatremia, hypercalcemia). Similarly, uncontrolled hypertension can induce metabolic (e.g., hypertensive encephalopathy) or structural (e.g., intracerebral hemorrhage) coma. Immunocompromised patients, especially those with poorly controlled human immunodeficiency virus (HIV) infection, are at higher risk for structural causes of coma including, CNS infections, and lymphoid malignancies.

**Physical Examination**

Physical examination is most helpful in differentiating structural from metabolic causes of coma when it reveals evidence of focal or lateralizing signs. In such patients, a metabolic etiology is uncommon.
(Exceptions to this rule occur in patients with hepatic failure, hypoglycemia, prior stroke, and postictal patients.) Comatose patients should always be fully disrobed and examined for evidence of occult trauma. Although physical evidence of head trauma suggests a structural cause, up to 50% of trauma patients also suffer from intoxication, often sufficient to produce coma. Boggy areas of the skull suggest depressed skull fracture, whereas the Battle sign (postauricular hematoma), “raccoon eyes,” and bloody nasal or aural discharge suggest basilar skull fracture. In traumatized patients, it is critical to exclude cervical spine instability before the neck is manipulated because serious spinal injuries commonly accompany cranial lesions severe enough to cause coma. Ecchymoses, mucosal bleeding, or petechiae may implicate coagulopathy and the potential for intracranial bleeding. Incontinence of stool or urine or tongue lacerations strongly suggest recent seizure. Atrial fibrillation, dilated heart, and recent myocardial infarction promote cerebral embolic disease. (Unless accompanied by seizure, embolic disease is an uncommon cause of coma because of the limited area of cerebral infarction usually caused by emboli.) Cardiac murmurs should raise suspicion of endocarditis-induced septic embolism or brain abscess. Arrhythmias only result in coma when they cause hypotension or cerebral emboli. In this setting, isolated carotid bruits are of little significance because occlusive carotid disease is a rare cause of coma. Nuchal rigidity suggests meningitis, encephalitis, or SAH.

The examiner must remain aware of the possibility of malingering or somatoform disorders. Veracity of the unresponsive state may be determined by a simple test of forced eyelid opening. Resistance by the patient to eyelid opening that increases with increasing effort by the examiner suggests a functional or feigned etiology of unresponsiveness. Another simple test is arm dropping, which is accomplished by release of the patient's arm from a starting point suspended over his or her face. In a conscious patient without motor deficits, the falling arm will deviate and not forcefully contact the face.

Vital signs provide additional clues to diagnosis. Although hypertension may accompany any cause of increased ICP, severe hypertension suggests subarachnoid or intracerebral hemorrhage, particularly if accompanied by nuchal rigidity or focal neurologic signs, respectively. Hypertensive encephalopathy alone is less likely to produce coma and is usually characterized by a nonfocal examination and blood pressures greater than 240/130 mm Hg. Stimulant intoxication with amphetamines, cocaine, phencyclidine, or phenylpropanolamine should also be considered in patients with altered mental status and hypertension. Cocaine may produce hypertension and delirium, but if coma is present in the absence of other overdosed drugs or obvious explanation, intracranial hemorrhage should be suspected. Although hypotension may also produce coma, young patients without underlying vascular or cerebral disease may remain awake with very low (40 to 50 mm Hg) MAPs. Elderly individuals, patients with chronic hypertension, and those with concurrent metabolic encephalopathy or structural lesions tolerate hypotension less well.

Heatstroke, serotonin syndrome, neuroleptic malignant syndrome, malignant hyperthermia, stimulant intoxication, and serious infections may cause fever sufficient to impair consciousness. Patients with hyperthermia or hypothermia frequently have an infection accompanying the primary temperature disorder that may itself disturb consciousness (e.g., pneumonia, brain abscess, or meningitis). Although primary aberrations of body temperature can directly cause coma, they rarely do so until core temperatures exceed 105°F or fall below 80°F (see Chapter 28). Bradypnea and hypoventilation most often result from the sedative effects of drugs or alcohol, accumulated hepatic or renal toxins, hypothyroidism, or far advanced brainstem compression. Tachypnea is a nonspecific finding but usually arises from one of four basic causes: (1) inappropriate ventilatory control, (2) hypoxemia, (3) respiratory compensation for metabolic challenges or increased dead space, and (4) reduced lung or chest wall compliance. Contrary to popular teaching, specific “pathognomonic” respiratory patterns have little localizing or prognostic value, with one notable exception—uncoordinated, irregular (ataxic) respiration usually indicates severe medullary
Expanded Neurologic Examination

After the vital signs are obtained, ventilation and perfusion are stabilized, and initial history and physical examination are performed, neurologic function should be examined in a stepwise fashion. The five key features of the initial neurologic examination may be remembered by the mnemonic “SPERM”: (1) State of consciousness, (2) Pupillary response, (3) Eye movements, (4) Respiratory rate and pattern, and (5) Motor function.

One of four terms should be used to describe the state of consciousness: (1) alert, (2) lethargic (aroused with simple commands), (3) stuporous (aroused only with vigorous stimulation—usually pain), and (4) comatose (unarousable).

Pupil size, congruency, and response to light and accommodation should be described. Pupillary function is controlled by the midbrain. Therefore, if the pupils function normally, the cause of coma either is a structural lesion located above the midbrain or is metabolic. Small “pinpoint” pupils usually result from pontine hemorrhage or from ingestion of narcotics or organophosphates. (Meperidine may fail to produce the miotic pupils typical of other narcotics.)

Pupillary responses remain intact in most metabolic causes of coma. Exceptions to this rule include atropine and atropine-like substances (such as certain tricyclic antidepressants). With uncal herniation from increased supratentorial pressure, the third cranial nerve is compressed against the tentorial edge, resulting in unilateral pupillary dilation and fixation. If increased pressure goes unrelieved, complete diencephalic herniation can occur resulting in bilaterally fixed midposition (3 to 5 mm) pupils.

Normal movement of the eyes requires an intact pontomedullary-midbrain connection. In comatose patients, the resting position of the gaze, the presence of nystagmus (horizontal, vertical, or rotatory), and the response to head movements (oculocephalic testing) or to cold tympanic membrane stimulation (oculovestibular testing) should be recorded. A normal response to oculocephalic testing is conjugate eye movement away from the direction of head rotation. A normal response to cold oculovestibular testing is conjugate eye movement toward the side of stimulation. Cervical spine stability must be ensured before oculocephalic maneuvers are performed. Likewise, tympanic membrane integrity should be confirmed before oculovestibular testing to prevent introduction of water into the cerebrospinal fluid (CSF) through a basilar skull fracture. Although endogenous toxins accumulated from hepatic or renal failure may not impair coordinated eye movements, exogenous toxins (drugs) frequently do. In addition, depletion of thiamine (Wernicke syndrome) can result in horizontal and vertical nystagmus. In pontine disorders, the medial longitudinal fasciculus is often dysfunctional, whereas sixth cranial nerve function is preserved. Therefore, ipsilateral eye abduction is intact, but contralateral adduction is impaired. Quite simply, if rotation of the head (oculocephalic) and vestibular stimulation (calorics) produce no change in eye position, the pons is nonfunctional. If only the eye ipsilateral to caloric stimulus abducts, a lesion of the medial longitudinal fasciculus (encapsulated by the pons) should be suspected.

Table 34-4. The Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Eyes</th>
<th>Open Spontaneously</th>
<th>4</th>
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<tbody>
<tr>
<td></td>
<td>To verbal command</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>To pain</td>
<td>2</td>
</tr>
</tbody>
</table>
The highest observed level of motor function should be noted (e.g., “Spontaneously moves all extremities,” “Withdraws only right arm and leg from noxious stimulus,” “No response to pain”). Motor function in pontine compression is often limited to extensor (decerebrate) posturing, whereas lesions above the pons can produce flexor (decorticate) posturing. If a structural lesion compresses the centers for respiration and heart rate control on the dorsal medullary surface, the patient also will be flaccid, without eye movements, and will have midposition, unreactive pupils. Although “posturing” is an ominous finding in most settings, rarely it can be observed as the result of metabolic encephalopathy (especially acute hepatic failure) and, in such cases, is completely reversible.

The results of the neurologic examination are often reported using a standardized scale. Currently, the Glasgow Coma Scale (GCS) is the most commonly used composite score. In this system, best motor, verbal, and eye opening responses are tallied in a score ranging from 3 to 15 (Table 34-4).

**Localizing the Level of Dysfunction**

If history or examination reveals a sequential, rostrocaudal loss of function, either a supratentorial mass lesion or diffusely increased ICP is the most likely etiology of coma. Funduscopic examination that demonstrates papilledema is also diagnostic of increased ICP or hypertensive encephalopathy.

Although the thalamus-diencephalon cannot be directly examined, injury to this area usually depresses consciousness but spares motor function. (Because pupillary and ocular movements are controlled by the midbrain and pons, respectively, they typically remain unaffected.) The respiratory pattern in thalamic dysfunction is unpredictable. In the rostrocaudal sequence, injury extending lower than the midbrain level usually results in loss of motor function and decorticate, or flexor, posturing. Although pupillary diameter is generally midposition (approx. 3 mm), midbrain injury tends to spare pupil reactivity as well as eye movements. When damage extends further to the pontine level, pupillary function is routinely impaired. Motor responses are often limited to extensor (decerebrate) posturing. If compression progresses to the medullary level, all motor function is usually lost, as are pupillary response and eye movements. It is only with medullary compression that respiratory rhythm is predictably affected, becoming ataxic.
**Laboratory Evaluation**

Blood and urine should be collected to evaluate potential metabolic and toxic causes of coma. Situation-appropriate testing is indicated, even in patients with obvious head trauma, because of the possibility that a metabolic cause may coexist or may have precipitated the injury (e.g., alcohol, carbon monoxide). Laboratory determinations should include indices of renal and hepatic function, serum glucose and electrolyte determinations, hemoglobin and arterial blood gases, and, when appropriate, carboxyhemoglobin determinations. If the history, physical examination, or initial laboratory testing suggests drug overdose or poisoning, a toxicology profile, and (if indicated) specific levels of compounds not included in a typical toxicology screen (e.g., aspirin, acetaminophen, ethylene glycol, methanol), should be obtained (see Chapter 33).

**Treatment**

The major diagnostic differential is to separate structural from metabolic causes of coma. However, in all cases, similar supportive treatment should be undertaken. The airway is secured, perfusion stabilized, and oxygen administered. The cervical spine requires immobilization if there is any suspicion of trauma. Reliable intravenous access should be established to obtain appropriate laboratory specimens and administer fluids and medications. Because of its time-sensitive importance, glucose levels should be tested at the bedside. If testing is not immediately available or if the measured glucose value is low, 50% dextrose in water (D50W) and thiamine (100 mg) are indicated, accompanied by magnesium and multivitamin preparations.

Naloxone, a narcotic antagonist, and flumazenil, a benzodiazepine antagonist, can temporarily reverse narcotic and benzodiazepine-induced coma, respectively, and thus serve as useful *diagnostic* tools. The duration of action of a bolus of either antagonist is less than that of its agonist counterpart; thus, neither compound is a reliable substitute for intubation and mechanical ventilation in patients with sedative-induced respiratory failure. Recurrent coma often follows a single dose of either reversing agent in patients who are not closely monitored.

After initial stabilization and primary evaluation, a more detailed neurologic examination and specific diagnostic testing can be undertaken. In most cases, a head CT scan will be performed (Fig. 34-3). In patients just admitted to the hospital with coma, the CT scan is much more likely to reveal a structural cause of coma than it would in patients who have been in the ICU for a period of time. (The important exception to this rule is the ICU patient who has a new focal deficit or first seizure.) Magnetic resonance imaging (MRI) scanning typically adds little to CT results. Occasionally, however, early changes indicating anoxia, subtle cerebral edema, venous sinus thrombosis, and acute ischemic strokes can be seen on MRI of a comatose patient with a nondiagnostic CT scan. In most febrile comatose patients, blood cultures, LP, and institution of antibiotics are indicated. However, if lateralizing neurologic signs are present or if there is a history of seizure, trauma, or immunocompromise, CT of the head should usually precede LP but not antibiotic administration. For patients with a clear metabolic cause of coma (e.g., hepatic or renal failure), organ-specific treatment should be undertaken; urgent dialysis of appropriate toxins (e.g., salicylates) may be indicated after overdose is clearly established.
FIGURE 34-3. Axial image of the head in a comatose patient. Large frontal and temporal hemorrhages on the left are identified with associated midline shift.

Prognosis
Surprisingly, the history and clinical examination over time are better predictors of outcome than sophisticated ancillary tests. Comatose patients destined to completely recover almost always show significant neurologic improvement within days. As a general rule, the faster the motor activity returns, the better the prospects for full recovery. With regard to etiology, drug-induced coma has an excellent prognosis. By contrast, the prognosis of persisting coma is poor if the etiology is ischemia or trauma.

SEIZURES

Pathophysiology
Seizures result from paroxysmal neuronal discharges that cause generalized or focal neurologic signs.
Many generalized seizures begin as a focal cortical discharge. Knowledge of the cell biology of seizures has advanced considerably. For example, we now know seizures are associated with excessive activity of \( N\)-methyl-D-aspartate (NMDA) receptors and inadequate stimulation of gamma-aminobutyric acid (GABA) receptors. Understanding the respective roles of these neurotransmitters helps explain the effectiveness of GABA stimulants as anticonvulsants.

Although seizures have been classified in many ways, it is probably most useful to think of them in terms of their duration (brief vs. continuous) and scope (generalized vs. focal). Duration is important because prolonged seizures often become progressively refractory to treatment, irreversibly injure neuronal tissue, and cause systemic metabolic problems (e.g., acidosis, hypoxia, hyperthermia, and rhabdomyolysis). Although there is no standard definition of the commonly used term “status epilepticus,” it is generally agreed that a single seizure lasting longer than 5 minutes or a series of recurring seizures without an intervening period of consciousness qualifies. Similarly, although not standardized, the term “refractory status epilepticus” has been applied to the potentially lethal situation in which seizures last longer than 2 hours or cannot be controlled with two or more anticonvulsants. Focality is also noteworthy because it suggests a discrete structural abnormality. Although seizures usually present as localized or generalized phasic muscle spasms, seizures that occur in the ICU occasionally masquerade as unexplained coma or puzzling sensory or psychiatric disturbances. Seizures in the critically ill often do not have a classic convulsive presentation. Conversely, although the typically generalized pattern of convulsive status epilepticus is rather easily identified, postanoxic myclonus, posturing during herniation, and psychogenic seizures must often be considered in the differential diagnosis.

Generalized convulsive status epilepticus is a relatively common neurologic emergency, with an overall incidence of 40 to 60 cases per 100,000 patients per year. Rapid diagnosis is essential, as untreated status epilepticus rapidly becomes refractory to therapy and carries significant morbidity and mortality. Classic clinical features include generalized and sustained tonic/clonic movements (rhythmic jerking) of the extremities together with mental status impairment (coma, lethargy, confusion); additional neurologic findings may include aphasia, amnesia, staring, blinking, facial twitching, agitation, nystagmus, eye deviation, and perseveration. After convulsions have ceased, focal findings such as localized motor impairment (Todd paralysis) may persist for hours afterward. The most important categorization of status epilepticus focuses on convulsive and nonconvulsive presentations, as these are most important to recognize for the emergency and ICU physician.

Status epilepticus must be distinguished from myoclonus, a problem most frequently seen after cardiac arrest. Both present with myoclonic jerks of the extremities, but only myoclonic status epilepticus is associated with epileptiform electrical discharges on the electroencephalogram (EEG). EEG findings of status myoclonic are slow waves or burst suppression patterns but no epileptiform discharges. Although sustained myoclonus occurs most frequently in the setting of anoxic brain injury, occasionally it may be encountered in conjunction with other encephalopathies, such as acute renal failure. The pathologic mechanism is related to subcortical white matter injury, specifically of the corticospinal tract. Symptomatic treatment includes benzodiazepines, valproic acid, and levetiracetam.

**Etiology**

Seizures arise from intrinsic electrical instability (epilepsy), toxic or metabolic disturbances (e.g., electrolyte imbalances, alcohol, drug effect), structural lesions (e.g., trauma or tumor), infectious causes (e.g., meningitis, cerebritis, brain abscess), or abnormalities of brain perfusion (global hypoxia). In general, these etiologic factors segregate into two prognostic groups. Patients with idiopathic epilepsy, subtherapeutic drug levels, and alcohol-
related seizures tend to have an excellent prognosis, whereas victims of stroke, trauma, tumor, encephalitis, or direct CNS poisons tend to have a poor outlook.

For the most part, seizures occur at the extremes of age, with the most frequent causes of seizures differing by age cohort. For example, children most commonly have seizures as the result of fever, infection, or a change in anticonvulsant medications used to treat idiopathic epilepsy. By contrast, young adults are much more likely to seize from SAH, trauma, noncompliance with anticonvulsants, or drug use or withdrawal (e.g., tricyclic antidepressants, cocaine, alcohol). In the older adult, stroke, subdural hematoma, and tumor become more common. Hypoglycemia and CNS infections (e.g., meningitis, encephalitis) may be causal at any age.

High fever (especially in children), drug withdrawal (particularly anticonvulsants, ethanol, barbiturates, benzodiazepines, baclofen), and iatrogenic overdoses of isoniazid, penicillin, imipenem, tricyclic antidepressants, theophylline, or lidocaine are typical metabolic causes. Electrolyte disturbances may also induce seizures, especially when such changes occur abruptly (e.g., acute hyponatremia or disequilibrium following hemodialysis).

Most seizure disorders that occur in outpatients are idiopathic, but this is true less often in the ICU, where such treatable conditions as drug or alcohol withdrawal, metabolic imbalances, drug toxicity, and acute structural lesions are more common. Most important among the metabolic precipitants are uremia, hypoglycemia, hypocalcemia, hypomagnesemia, and hyponatremia. Meningitis, encephalitis, and brain abscess are frequent causes of seizure; about one third of adults with bacterial meningitis will experience a seizure. HIV predisposes to seizure-inducing CNS infections that include toxoplasmosis and viral encephalitis.

### Diagnosis

A seizure diagnosis is usually made from the history and observation of an attack. Occasionally, historical features and/or the clinical appearance are so atypical as to require confirmation by electroencephalography (EEG). In such cases, an intraictal EEG may be diagnostic and the pattern of discharge may help determine etiology. For example, EEG localization of seizure discharge to the base of the temporal lobes (or appropriate MRI findings) suggests herpes encephalitis. EEG recording may also reveal seizure activity in a patient with unexplained coma.

A sustained period of continuous EEG complemented by simultaneous video monitoring may be needed to detect seizure or distinguish between myoclonus and focal seizures. In fact, up to 20% of unresponsive ICU patients may have occult seizures, and an even higher percentage (50%) of patients who remain unresponsive after having a convulsion have been found to have ongoing nonconvulsive seizures. A head CT or MRI scan is indicated for new-onset seizures, those accompanied by a preceding or persistent focal neurologic deficit, and in those refractory to simple medical therapy. In such patients, a CT often reveals a structural cause (e.g., vascular malformation, primary or metastatic tumor, or subdural subarachnoid or parenchymal hemorrhage).

In patients with a known seizure disorder, a CT scan is not necessary to evaluate each recurrence; however, it should be remembered that even patients with previously diagnosed epilepsy develop strokes, tumors, and CNS infections. Hence, recurrent seizures, especially when observed in an altered presentation or accelerating pattern of occurrence, should not be reflexly ascribed to a singular predetermined cause.

### Systemic Effects of Seizures

Brief ictal episodes are of little consequence provided that they do not occur while the patient is involved in a
dangerous activity and that the airway, oxygenation, and ventilation are preserved. However, continuous electrical firing during prolonged seizures depletes cellular reserves of oxygen and adenosine triphosphate (ATP) and allows intracellular accumulation of calcium, all processes that culminate in neuronal death. By damaging the cortex, recurrent or prolonged seizures are associated with long-term cognitive impairment. In humans, seizures ≥2 hours in duration reliably result in brain injury, but lasting injury may begin as early as 30 minutes after seizure onset. Seizure-induced neuronal damage does not require loss of consciousness nor convulsive muscular contraction. Finally, in high-risk settings, the possibility of occult (masked) seizures is wise to bear in mind when deep neuromuscular blockade is required to assist mechanical ventilation.

Massive catecholamine release during generalized convulsions may induce arterial and intracranial hypertension and pulmonary edema. Adrenergic stimulation initially produces hyperglycemia, but glucose is rapidly consumed during prolonged seizures, with the attendant risk of hypoglycemia. Central thermostatic reset and/or sustained muscular activity may boost body temperature to concerning levels (>105°F), and such fevers tend to respond poorly to antipyretics. Furthermore, thermoregulation may be disturbed for days after seizure cessation. Because fever and leukemoid reactions (peripheral leukocyte counts often exceed 20,000 cells/mm³) are common, infection is often suspected. Differentiating infectious fever from convulsive fever is further confounded by the common occurrence of cerebral fluid pleocytosis with total leukocyte counts up to 80 cells/mm³ and a predominance of neutrophils.

Profound and rapid onset acidosis often accompanies generalized seizures. Approximately half of postictal acidicemic patients exhibit lactic acidosis alone, whereas the other half have a mixed respiratory and metabolic acidosis. Although the seizure-associated acidosis may be severe (pH < 6.5), no evidence links pH abnormality with outcome, and most patients resolve the acidosis within 1 hour. The same vigorous muscular contractions causing acidosis can result in rhabdomyolysis with hyperkalemia. Increased free water losses from sweating and hyperventilation may increase serum osmolarity and Na⁺ concentration. Hypotension and (rarely) seizure-induced cardiovascular collapse can further aggravate neurologic damage, but unlike the setting of ischemic brain injury, cerebral blood flow is typically increased in seizing patients. Direct neuronal damage from unrelieved electrical discharging, together with the metabolic pandemonium of status epilepticus, contributes to a significant mortality risk.

**Treatment**

The most important factors determining the outcome of status epilepticus are the etiology of the episode and the time required to terminate the seizure. Many patients (=2/3) have a history of seizures. Half of these patients are not compliant with antiepileptic drugs. Protection of the airway, oxygenation, and maintenance of perfusion are primary considerations. Aspiration risk can be reduced by proper patient positioning (lateral decubitus) and endotracheal intubation when clinical judgment dictates. If pharmacologic paralysis is necessary for intubation, short-acting agents are used, and EEG monitoring assumes greater importance because muscular activity will be halted but neuronal discharges can continue unrecognized. As with all causes of altered consciousness, electrolytes and glucose should be tested and normalized. Thiamine (100 mg) should be administered in most cases as a low yield but no risk measure to prevent Wernicke encephalopathy.

In patients who experience a solitary seizure or several brief seizures with known precipitant, long-term anticonvulsants are not always necessary; however, there is universal agreement that status epilepticus should be pharmacologically ended as rapidly as possible. Drugs that bind and stimulate GABA receptors are the most effective drugs for control of seizures. One strategy for management of status epilepticus is suggested in Table 34-5. There is no single ideal drug regimen for terminating seizures; however, benzodiazepines, specifically lorazepam, represent excellent initial choices because of their effectiveness,
rapid action, and wide therapeutic margin. Benzodiazepines cannot be expected to provide long-term seizure control by themselves, but can “break” seizures long enough to accomplish intubation if necessary and to initiate therapy with another longer-acting drug.

Initial intravenous doses of lorazepam (4 mg) are very effective in terminating seizure activity. The 2- to 3-hour half-life of lorazepam and avid GABA receptor binding provide seizure protection for up to 24 hours. Diazepam is an acceptable alternative. Benzodiazepines are frequently underdosed because amounts required in status epilepticus are greater than those used for most indications other than seizures. Other causes of initial treatment failure are inadequate initial doses of intravenous benzodiazepines and then waiting too long to repeat doses or advance to second-line agents or general anesthesia. Second-line medication options for patients with ongoing status epilepticus unresponsive to benzodiazepines include phenytoin and fosphenytoin, phenobarbital, valproate sodium, and levetiracetam.

### Table 34-5. Therapy of Status Epilepticus

<table>
<thead>
<tr>
<th>Step 1—Stabilize Vital Signs</th>
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<tbody>
<tr>
<td>Establish an airway, administer oxygen</td>
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<tr>
<td>Ensure circulation with adequate blood pressure</td>
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<tr>
<td>Establish intravenous access</td>
</tr>
<tr>
<td>Collect blood for electrolytes, glucose, hemoglobin, creatinine, liver function tests, acid-base status, and possibly toxicologic analysis</td>
</tr>
<tr>
<td>Administer D50W (1 mg/kg) and thiamine (1 mg/kg) unless patient known to be normoglycemic or hyperglycemic</td>
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<tr>
<th>Step 2—Rapidly Achieve Seizure Control</th>
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<tbody>
<tr>
<td>Lorazepam 4 mg IV, may repeat</td>
</tr>
<tr>
<td>Diazepam 5 mg IV, may repeat</td>
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<tr>
<td>Midazolam 10 mg IM</td>
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<table>
<thead>
<tr>
<th>Step 3—Achieve/Maintain Seizure Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin 20 mg/kg IV at 50 mg/min</td>
</tr>
<tr>
<td>Fosphenytoin 20 mg/kg IV (Phenytoin equivalents) at 150 mg/min</td>
</tr>
<tr>
<td>Valproate Sodium 20-40 mg/kg IV over 10 min; if still seizing, give additional 20 mg/kg IV over 5 min</td>
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<tr>
<th>Step 4—Salvage Therapy for Resistant Status Epilepticus</th>
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</thead>
<tbody>
<tr>
<td>Propofol—1-2 mg/kg IV q 3-5 min up to 10 mg/kg, then infuse 30-200 μg/kg/min</td>
</tr>
<tr>
<td>Midazolam—0.2 mg/kg, then boluses 0.2-0.4 mg/kg q 5 min up to 2 mg/kg, then infusion 0.05-2 mg/kg/h</td>
</tr>
<tr>
<td>Pentobarbital—5-15 mg/kg IV up to 50 mg/min with repeated 5-10 mg/kg boluses until seizures stop, then infusion 0.5-5 mg/kg/h</td>
</tr>
<tr>
<td>General anesthesia</td>
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</table>
Among second-line agents, the preferred medications have been intravenous 20 mg/kg of phenytoin at rates up to 50 mg/min or fosphenytoin given at rates up to 150 mg/min. Phenytoin and fosphenytoin are FDA-labeled for treatment for status epilepticus in adults. Fosphenytoin is a watersoluble prodrug that is converted to phenytoin by plasma esterases. Phenytoin, but not fosphenytoin, is labeled for status epilepticus in children. Both of these agents act at the sodium channel rather than the GABA receptor and, therefore, represent rationale choices for treating patients whose seizures do not terminate with benzodiazepine GABA agonists. Bradycardia and hypotension may occur at high infusion rates with phenytoin and fosphenytoin, particularly in the elderly or in those with significant cardiac disease. Small randomized trials suggest that intravenous valproate sodium may have similar efficacy in status epilepticus when compared to phenytoin. Valproate sodium up to 40 mg/kg is given intravenously over 10 minutes with an additional 20 mg/kg given over 5 minutes if the patient continues to seize. Valproate sodium probably has fewer cardiopulmonary side effects than phenytoin and may be preferred in patients with hypotension or respiratory distress.

Intravenous pentobarbital is also FDA-labeled for the treatment of status epilepticus and remains a viable option. It is now less commonly used in adults unless other agents are contraindicated or unavailable. Phenobarbital (20 mg/kg) intravenously is given at 50 to 100 mg/min with an additional 5 to 10 mg/kg if needed. Phenobarbital also acts at the GABA receptor and therefore may be a less rationale choice in patients who have not responded to benzodiazepines. Levetiracetam is often used as a second-line agent to treat status epilepticus and can be given as a 1- to 3-g dose intravenously over 5 minutes or 2 to 5 mg/kg/min. These and other second-line agents may be used to suppress recurrent seizures in patients after status epilepticus has ended.

If seizures have stopped and the patient has awakened, loading doses of antiepileptic medications with longer half-lives should be initiated and given either intravenously or orally. A single loading dose of phenytoin (20 mg/kg) may result in therapeutic levels within 3 hours. For patients requiring intravenous loading, fosphenytoin, valproate sodium, and levetiracetam may be considered. When the patient has not awakened, EEG monitoring is useful. The most important cause for persistent stupor after convulsive status epilepticus is ongoing electrical seizures, which may only be detectable by EEG monitoring.

Status epilepticus is almost always terminated by the primary and secondary drugs described above. If the patient remains in status epilepticus, however, general anesthesia and drug-induced coma are recommended. It is not advisable to delay advanced therapy with repeated trials of alternative second tier antiepileptic drugs. In general, 30 to 60 minutes is adequate to determine if primary and second-line agents are successful. Endotracheal intubation is necessary to allow induction of therapeutic coma, and this and other supportive measures should rapidly be performed in the patient with refractory status epilepticus. In the setting of neurologic blockade performed for purposes of coordinating with mechanical ventilation, it is advisable to use continuous EEG monitoring.

Agents most commonly used to induce general anesthetic state of coma are continuous infusions of midazolam or propofol. Intravenous midazolam infusions are usually preceded with a loading dose of 0.2 mg/kg at 2 mg/min with repeated doses of 0.2 to 0.4 mg/kg every 5 minutes until seizures stop up to a
maximum loading dose of 2 mg/kg. Continuous infusion of midazolam should then be started at 0.05 to 2 mg/kg/h. Intravenous propofol infusions usually include a loading dose of 1 to 2 mg/kg over 3 to 5 minutes with repeated boluses of the same amount of drug every 3 to 5 minutes until seizures stop up to a maximum total loading dose of 10 mg/kg. Propofol infusion should then be maintained at 30 to 200 µg/kg/min. Hypotension is very common at higher doses.

Pentobarbital is an acceptable alternative agent for the treatment of refractory status epilepticus. Pentobarbital has significant side effects including hypotension and prolonged half-life. Use of pentobarbital infusion requires careful cardiopulmonary monitoring. When intravenous pentobarbital is employed, a loading dose of 5 to 15 mg/kg intravenous is given at a rate up to 50 mg/min with repeated 5 to 10 mg/kg boluses until seizures stop and then at a maintenance rate of 0.5 to 10 mg/kg/h.

As already noted, most medications for treatment of status epilepticus may cause dose-dependent hypotension requiring intravenous vasopressors. With this in mind, a useful option in refractory status epilepticus is ketamine. Intravenous valproate sodium may preferentially be used in patients with status epilepticus who cannot or should not be intubated.

If “salvage” therapy is required for seizure control, availability of EEG monitoring and expert neurologic consultation are essential. Unfortunately, there is no consensus for EEG endpoints of therapy; trained electroencephalographers are never continuously available; and most ICU physicians lack specialized skill in EEG interpretation. With regard to goal setting, seizure control certainly does not require achieving an “isoelectric” EEG; the value of achieving a “burst suppression” pattern is even questioned. Simply preventing organized seizure activity is an adequate endpoint in most cases. So the question arises, how does a critical care doctor recognize seizure activity on EEG? Although hardly a substitute for formal training, a couple of simple guidelines are useful. A normal EEG demonstrates asymmetric, high-frequency, low-amplitude waveforms in multiple channels; perhaps to most critical care physicians, the best description of a normal EEG might be that it looks like “ventricular fibrillation.” Anytime symmetric, large magnitude discharges, or for that matter if any recognizable pattern can be identified on EEG, seizure activity should be suspected.

**STROKE**

Cerebrovascular accident or stroke is a common cause of death and a frequent reason for ICU admission. The unifying factor in all stroke syndromes is neuronal ischemia because of interruption of blood flow. The term stroke, from biblical reference to being “struck down,” implies an acute dramatic event. Although sudden profound neurologic events are the rule, in the ICU population, the presentation is often more subtle and atypical. Common occurrences such as altered mental status, delayed awakening from sedation, slurred speech, decreased level of consciousness, agitation, or the new onset of seizures may be the only manifestation of stroke. In hospitalized patients, many strokes are the result of treatment-related cerebral emboli or hemorrhage rather than acute thrombosis.

<table>
<thead>
<tr>
<th></th>
<th>Embolic</th>
<th>Thrombotic</th>
<th>Hemorrhagic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time course</td>
<td>Abrupt, maximal deficit at onset</td>
<td>Abrupt, maximal deficit at onset</td>
<td>Prodromal headache Abrupt, rapid progression</td>
</tr>
</tbody>
</table>
### Occasional dramatic improvement
- Occasional brief improvement
- Sudden loss of consciousness

### Common deficits
- Cortical infarcts
- Cortical infarcts
- Internal capsule, basal ganglia

### Predisposing factors
- Older Caucasian
- Atrial fibrillation
- Arterial catheter flushing
- Mitral stenosis
- Cardiac catheterization
- Central venous catheter insertion
- Endocarditis (esp. fungal)
- Atrial septal defect
- Left ventricular dilation
- Older Caucasian
- Heart failure
- Hypercholesterolemia
- Hypertension
- Smoking
- Diabetes
- Younger Black and Asian
- Hypertension
- Vascular malformation
- Amphetamine, cocaine, phenylpropanolamine
- Anticoagulant use

### Antecedent history
- Recent myocardial Infarction
- DVT-pulmonary embolism
- TIA common
- Amaurosis fugax
- Central retinal artery occlusion
- Recent thrombolytic therapy
- “Herald bleed”

### Therapy
- Antithrombotic
- Thrombolytic (early)
- Elective endarterectomy
- Correction of coagulopathy
- Surgical evacuation of selected lesions

---

### Pathophysiology

Two pathophysiologic mechanisms account for almost all strokes: *ischemia* from occlusive thrombosis, embolism, or systemic hypoperfusion and *hemorrhage* into brain tissue or the subarachnoid space. Although occlusion of venous drainage (rather than arterial blockage) can also lead to ischemia, strokes from that mechanism occur rarely and in very specific situations (e.g., paranasal sinus infection, thrombophilia, sickle cell disease). Each of the common stroke syndromes summarized in Table 34-6 has its own predisposing factors, typical clinical presentation, and specific treatment.

---

### Initial Evaluation

For patients with stroke, time to definitive treatment is the largest controllable determinant of outcome. Because the treatments of ischemic stroke, hemorrhage stroke, and other common disorders that mimic stroke (Table 34-7) are drastically different, it is essential to promptly make a firm diagnosis. Efficiency of care and outcomes are improved by establishing teams of experts who evaluate patients with suspected stroke in a stereotypical fashion, which includes a directed history and physical examination, concise laboratory evaluation, and urgently obtained brain imaging. Essential historical elements are (1) the time the patient was last known to have normal neurologic function, (2) recent trauma or surgery, and (3) medications used, especially anticoagulants,
anticonvulsants, antihypertensives, antiarrhythmics, and diabetic agents. Initial examination should evaluate the heart and arteries and search for signs of liver disease, bleeding, and coagulopathy. Neurologic evaluation should be performed using a standardized tool like the National Institute of Health Stroke Scale (NIHSS), which provides a quantitative measure of stroke-related neurologic deficit that considers level of consciousness, ability to follow commands, language function, attentiveness or neglect, visual fields, horizontal eye movements, facial asymmetry, motor strength, sensation, and coordination. This informative examination may be performed rapidly by the nonneurologist (https://www.ninds.nih.gov/sites/default/files/NIH_Stroke_Scale_Booklet.pdf).

<table>
<thead>
<tr>
<th>Table 34-7. Mimics of Stroke Syndromes</th>
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<tbody>
<tr>
<td>Migraine</td>
</tr>
<tr>
<td>Seizures and postictal period</td>
</tr>
<tr>
<td>Intoxication</td>
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<tr>
<td>Hyponatremia</td>
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<tr>
<td>Hypoglycemia</td>
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<tr>
<td>Brain tumor or metastases</td>
</tr>
</tbody>
</table>

While the history and examination are performed, appropriate laboratory studies, including electrolytes, glucose, creatinine, hemoglobin, platelet count, and coagulation profile, should be obtained. This battery of tests is used to bring important nonstroke mimics and coagulopathies into consideration and to provide a baseline for as well as determine safety of thrombolytic therapy, if indicated. An electrocardiogram to evaluate cardiac rhythm and the possibility of ischemia is also prudent. Even though the yield of a chest radiograph is low, it is a rapid, inexpensive, safe test to screen for abnormalities of the aorta and to look for intrathoracic neoplasm as a potential source of metastases.

After initial stabilization, immediate head imaging is indicated to evaluate the type and magnitude of stroke. There remains some debate concerning the best initial imaging study; however, a noncontrast CT scan is obtained rapidly and is almost always adequate for key decision-making. Early after ischemic stroke, CT may be normal. A normal CT rules out acute hemorrhagic stroke. Many centers now perform cranial CT angiography, which can better characterize an occlusive lesion. If for logistical reasons MRI scanning can be accomplished faster (rarely the case), it is an acceptable alternative. In suspected brainstem stroke, MRI may add valuable information to CT scan data. MRI will demonstrate ischemic stroke before CT (see Chapter 11). A general pathway for initial care of the stroke patient is presented in Figure 34-4. A complete ischemic stroke is shown in Figure 34-5.

**General Care of the Stroke Patient**

The therapy of each specific stroke syndrome depends on its etiology and structural manifestations. All, however, benefit from assiduous supportive care. Because of the frequency of serious complications in stroke victims, standard prophylactic measures to prevent skin breakdown, gastric ulceration, and deep venous
thrombosis (DVT) make especially good sense. One to two weeks of prophylactic anticonvulsant therapy may be useful for persons with large hemorrhagic strokes. Regardless of etiology, all stroke patients should have oxygenation and perfusion evaluated upon arrival. If saturations are below normal, supplemental oxygen should be administered; however, maintaining abnormally high PaO$_2$ does not benefit—and may (through microvascular constriction) harm—patients with normal arterial saturation. Symptomatic arrhythmias, particularly those causing hypotension, should be immediately corrected. Although there are little high-quality data to support the practice, anemia is usually corrected to a hemoglobin level ≥10 g/dL.

The appropriate target range for blood pressure in stroke victims varies somewhat with cause and chronic baseline. Worse outcomes are associated both with hypotension and hypertension. Transient, moderate hypertension (systolic BP >160 mm Hg) is nearly universal in all forms of stroke, as is a gradual spontaneous decline in pressure that occurs over the first day of illness. Because self-correction is common, caution should be used to avoid overtreatment. Rapidly lowering blood pressure or “normalizing” blood pressure in the chronically hypertensive stroke victim is likely to do more harm than good. As a general rule, unless the patient is treated with thrombolytic therapy, or has pulmonary edema, myocardial infarction, or aortic dissection, blood pressures less than 220/120 mm Hg should not be treated. Blood pressure greater than 220/120 mm Hg or where thrombolytic therapy is considered may be managed with nicardipine or labetalol. (If thrombolytic therapy is used, a goal of <185/110 mm Hg is recommended.) Unless causing immediate harm, gradual reduction in blood pressure over several hours to days using oral antihypertensive therapy is probably the best course of action. If pharmacotherapy is chosen, drugs without CNS depressant effects are preferred. Within a few days of the stroke, a reasonable low-end target for MAP is 110 to 120 mm Hg. A discussion of blood pressure control is presented in Chapter 22.

The importance of glucose control is debated. Older studies show an association of hyperglycemia with poor neurologic outcome; however, it is very possible that hyperglycemia is only a marker of severity of brain injury rather than a proximate cause of damage; no cause-and-effect relationship between mild hyperglycemia and brain injury has actually been proven or physiologically rationalized. As a general principle, even transient hypoglycemia is likely to be more harmful than sustained mild hyperglycemia. Use of a standardized protocol that frequently monitors glucose values, uses short-acting insulin, and aims for nearly normal levels (<140 to 180 mg/dL) is currently advocated. An overview of stroke therapy is provided in Figure 34-4 and discussed in detail below.
FIGURE 34-4. Initial Management of Acute Stroke. ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery.
Ischemic Stroke

Ischemic strokes, the most common and important variety, typically result from the progressive occlusion of larger arteries (usually, branches off the carotid). The incidence of ischemic stroke relates to increasing age as the chronic risk factors of heredity, diabetes, hypertension, smoking, and hypercholesterolemia take their toll on vessel patency. (Thrombophilia, migraine, arterial dissection, and fibromuscular dysplasia are much less common causes of thrombosis.) Although large vessels are usually the target, ischemic strokes can occur in small perforating vessels, resulting in a specific pattern known as a “lacune.” Stroke may also occur in patients with less-than-critical vascular narrowing when hypotension, hypoxemia, or coagulopathy tips the balance of cerebral oxygen supply and demand unfavorably. When brain perfusion is impaired globally (e.g., shock, cardiopulmonary arrest), regions at the border between two vascular distributions suffer the greatest insults. Ischemia of these so-called watershed zones results in three major clinical syndromes including (1) bilateral upper extremity paralysis, (2) cortical blindness, and (3) memory impairment.

Slow progressive vessel narrowing can result in premonitory ischemic episodes and transient ischemic attacks (TIAs). Although technically the neurologic deficits of a TIA can last up to 24 hours, most resolve in less than 10 minutes. Akin to unstable angina, TIAs serve as markers of a transition period during which stroke is likely. The risk of stroke correlates with the severity of the TIA—when temporary monocular vision loss (amaurosis fugax) is the only symptom, the risk of stroke is substantially lower than when large hemispheric defects occur. A TIA is a powerful warning sign that must not be ignored because at this stage, antithrombotic therapy or radiological or surgical intervention can often abort a fatal or disabling stroke.

Up to one third of TIAs produce demonstrable injury on MRI. Although such cases are now classified as stroke, it is unlikely that any reperfusion therapy will be productive because tissue injury is already present and all symptoms have typically resolved. Approximately 50% of patients with a TIA will have CT findings of a prior event even though the stroke may have been clinically silent. A general approach to the patient with TIA is presented in Figure 34-6.

Scoring systems have been developed to segregate low-risk from high-risk TIAs. For low-risk
patients, outpatient evaluation in the days following presentation of symptoms may be appropriate, accompanied by administration of aspirin (325 mg) or clopidogrel (75 mg/d) or a combination of aspirin and dipyridamole. These patients should be started on a statin, evaluated for atrial fibrillation, receive carotid imaging, and be considered for transthoracic echocardiography if there is suspicion of a cardiac embolic source of TIA. If atrial fibrillation is identified, low molecular weight heparin or aspirin should be administered. For patients with high-risk TIA, continuation in hospital is appropriate. When present, moderate hypertension is accepted initially and gradually reduced thereafter.

FIGURE 34-6. Management of transient ischemic attack (TIA). ASA, acetylsalicylic acid; MRA, magnetic resonance angiography.

Because ischemic strokes usually infarct the cerebral cortex, where sensory and motor functions are anatomically juxtaposed, equal regional losses of sensation and motor function are the rule. This is in contrast to small-vessel strokes (lacunes), occurring deeper in the brain, where by virtue of the neuronal pathway arrangement, widespread deficits of isolated sensory or motor function are possible. For ischemic strokes, the supply distribution of the occluded vessel determines the pattern of neurologic deficit, which differs for the
anterior, middle, and posterior cerebral artery circulations. Typically, ischemic strokes present with a near immediate maximal deficit, often noted upon awakening.

When middle cerebral artery (MCA) flow is interrupted, the resulting sensory and motor deficits are greatest in the contralateral side of the face with lesser deficits in the arm and leg. MCA occlusions of the dominant cortex may also produce an expressive or receptive aphasia when damage occurs to the anterior or posterior speech centers, respectively. A corresponding lesion of the nondominant hemisphere may produce an acute, agitated, or confused state with contralateral motor and sensory deficits. Homonymous hemianopsia and conjugate eye deviation toward the side of the lesion are less common but characteristic features of MCA occlusion.

Occlusion of the anterior cerebral artery produces the greatest neurologic deficit in the contralateral leg, followed in severity by the arm and then face. A homonymous hemianopsia or loss of vision ipsilateral to the stroke is also possible. Frontal lobe signs of incontinence, grasp and suck reflexes, and perseveration are also common. Posterior cerebral artery ischemia does not usually impact the major centers for speech or motion; deficits are limited to homonymous hemianopsia, impaired recent memory, and prominent sensory loss.

For patients with a moderate to severe deficit or worse, intravenous thrombolysis, specifically using recombinant tissue type plasminogen activator (rtPA), should be considered for patients in whom it can be administered within 4.5 hours of onset of stroke symptoms. Prior to administration of rtPA, the clinician must evaluate indications and contraindications for its use (see Chapter 23). Recent trials have demonstrated that when administered at 0.9 mg/kg, IV rtPA tends to improve clinical outcomes for patients within 3 to 4.5 hours of stroke onset. After administration of rtPA, patients should not receive antiplatelet therapy or anticoagulation for 24 hours. Following this, patients may be started on aspirin and prophylaxis for deep vein thrombosis if no significant hemorrhagic transformation is visualized on a 24-hour follow-up CT scan of the head, a study that should be obtained in each patient.

Until recently, the use of endovascular therapy was limited to patients who were ineligible for IV rtPA, patients who failed to improve with the use of IV rtPA, and those who were carefully selected via MRI and CT perfusion to have large ischemic penumbra and only a small infarct core. Multiple recent trials, however, demonstrated benefit with the use of endovascular therapy during acute ischemic stroke for patients who present up to 24 hours after onset of symptoms and have large proximal artery occlusions. Thus, patients with proximal cerebral arterial occlusion who present up to a day after symptom onset may be considered for endovascular interventions in addition to rtPA, which is given in the initial hours if possible.

Successful recannulation of an artery can reduce the volume of tissue affected by stroke and subsequently reduce the need for critical care. As noted above, critical care interventions after recannulization include airway and respiratory management, blood pressure control, prevention of bleeding, seizure management, glycemic control, management of cerebral edema, and temperature control. If neurologic function deteriorates after administration of intravascular therapies, these interventions should be stopped, coagulation status corrected, and a repeat CT scan of the head obtained. Neurosurgical consultation is essential if intracranial hemorrhage is identified.

Aspirin reduces the incidence of thrombotic strokes when given prophylactically (particularly to patients with premonitory transient ischemia) and decreases the incidence of recurrent stroke. Unfortunately, aspirin does not abort stroke in progress or reverse established neurologic deficits. Among patients with ischemic stroke who are not candidates for thrombolytic treatment, aspirin therapy should be started within 48 hours.

The outcome of ischemic stroke is not improved by therapeutic hypothermia, heparin anticoagulation, or surgery. Carotid endarterectomy is not indicated for treatment of acute ischemic stroke, but in patients with chronic or recurrent symptoms of cerebral ischemia, endarterectomy may be beneficial. Endarterectomy is of proven benefit
if performed by an experienced surgeon in symptomatic patients with significant carotid stenosis and low operative risk. When the stenosis is less severe, endarterectomy is still probably acceptable provided the operative risk remains low. The surgeon's morbidity and mortality rate must, however, be low to favor surgical intervention in the asymptomatic patient.

**Embolic Strokes**

Embolic strokes result from the sudden impaction of a plug in a small cerebral artery branch, usually giving rise to isolated ischemic cortical defects. Because complete small-vessel occlusion occurs nearly instantaneously, maximal neurologic deficits are typically observed at the time of embolization, but it is common for deficits to partially, sometimes even dramatically, improve within 1 to 2 days. Because of the embolic nature of the injury, multiple discrete areas of the brain may be injured simultaneously. Although embolic strokes are considered to be second in frequency to thrombosis in the general population, patients in the ICU are at substantially higher risk of emboli because they are commonly subjected to procedures that predispose to arterial injury or thrombosis and cholesterol or air embolism (e.g., central venous catheterization complications, left heart catheterization, aortic balloon pump insertion, and invasive blood pressure monitoring). During such procedures, air, clot, or atherogenic material can be released or dislodged.

Cerebral embolism can result from foreign bodies, infected material, bland clot, air, or cholesterol fragments. Bland clots are formed either in a sluggishly flowing carotid system or within a heart having mural thrombi, myocardial infarction, mitral valve disease, or atrial fibrillation. Rarely, venous thromboemboli cause stroke as they cross a right-to-left intracardiac shunt entering the cerebral circulation (i.e., paradoxical embolism). In most cases, the intracardiac defect is a patent foramen ovale or atrial septal defect. Left-sided endocarditis is another potential source of embolism in the critically ill patient. Bacteria, fungi, and amorphous material sloughed by structurally abnormal or infected heart valves can all cause cerebrovascular plugging. It is not widely appreciated that arterial pressure generated when “flushing” a peripheral arterial line can exceed systolic blood pressure. Although rare, a sustained flush can propel clot or air retrograde into the cerebral circulation. Cerebral air emboli can result from disruption of the pulmonary veins by penetrating trauma or high ventilator inflation pressures, therapeutic misadventures during cardiac catheterization, rapid ascent from underwater diving, or unusual sexual practices (predominately in pregnant women).

The diagnosis of embolic stroke is usually not difficult to make. History most often reveals one or more predisposing conditions. In addition, the neurologic deficit is typically described as unexpected, immediate, and maximal in severity at onset. Because the heart is the most common embolic source, clinical examination often provides evidence of cardiac disease (e.g., atrial fibrillation, murmur, or cardiomegaly). Neurologic evaluation typically reveals a cortically based deficit with both sensory and motor losses to the same body region.

The CT scan is often unremarkable because the volume of tissue infarcted may be small. In patients with a history suggestive of embolic stroke without an obvious source, the combination of blood cultures to exclude endocarditis, cardiac monitoring to exclude arrhythmias, and a transthoracic echocardiogram to diagnose aortic atheromatous disease, mural thrombi, and valvular lesions and to evaluate myocardial performance constitutes a good initial diagnostic battery. Because of the superior sensitivity of transesophageal echocardiography (TEE) in finding subtle valvular lesions and small clots in the left atrial appendage, TEE should be considered in a patient with a history suggestive of embolism that has a nondiagnostic transthoracic echocardiogram. If symptoms localize to the carotid circulation and a cardiac source cannot be found, evaluation of the carotid branches should be undertaken using duplex ultrasound of the neck and transcranial Doppler. If symptoms are in the posterior circulation, evaluation of the origins of the vertebrobasilar and posterior cerebral arteries should be
Therapy of embolic stroke is dictated by the nature of the embolized material and by the size of the resulting lesion. Antimicrobial therapy is indicated in patients with emboli secondary to infective endocarditis. Valve replacement should be considered when large vegetations are present or when embolism recurs despite appropriate therapy. In patients with nonhemorrhagic embolic stroke from a cardiac source, heparin or low molecular weight heparin (LMWH) followed by warfarin with a target INR of 2 to 3 is indicated. Commonly, anticoagulation is delayed after the event to document absence of hemorrhage by follow-up CT scan. For patients with atrial fibrillation, long-term warfarin has been demonstrated to reduce the risk of stroke, particularly in the elderly. Oral anticoagulation with newer agents appears to offer excellent alternatives in patients without valvular heart disease.

**Lacunar Strokes**

Lacunes are ischemic events of tiny vessels deep within the brain, usually occurring in hypertensive individuals. Lacunar syndromes can result from bland infarction or hemorrhage. Most often, these events occur in the region of the internal capsule, producing a large functional deficit even though only a small area of brain is injured. Because neurons controlling distant body regions are closely grouped together, deficits of the face, arm, and leg are typically equal in severity. Similarly, because of the anatomic arrangement of neurons in this region, selective deficits of sensory or motor function can occur. This pattern of deficits is in distinct contrast to cortical infarcts where sensory and motor losses tend to occur in parallel and the limbs and face are usually affected to varying degrees.

**FIGURE 34-7. Axial, coronal, and sagittal images of cerebellar hemorrhagic stroke.**

The CT scan may be normal or show only a small lucency or density in patients with lacunes because of the typically small size of the infarct. MRI may be more informative. With the exception of appropriate supportive care and blood pressure control, there is no specific therapy for a lacunar infarct.

**Hemorrhagic Stroke**

Hemorrhagic strokes most commonly occur in the putamen, internal capsule, thalamus, caudate nucleus, pons, and cerebellum when small vessels rupture as the result of chronic hypertension or defects of the vessel wall (Fig. 34-7). Bleeding into the hemispheric parenchyma is less frequent and more commonly the result of excessive therapeutic anticoagulation, arteriovenous malformation, or venous hemangioma.

**Table 34-8. Sites and Characteristics of Intracerebral Hemorrhage**
Nonvascular risk factors may contribute to the development of hemorrhagic stroke. Extracranial risk factors include drug use (prescription or illicit) and systemic vasculitis. Therapeutic warfarin and heparin may account for intracranial hemorrhage as may thrombolytic therapy for acute myocardial infarction or ischemic stroke. Cocaine and amphetamines cause hemorrhage by increasing blood pressure or inducing vasculitis.

The site, relative frequency, and clinical characteristics of hemorrhagic stroke are presented in Table 34-8. The deficits created by intracerebral hemorrhage are usually rapidly progressive, but late deterioration can be seen days after the initial bleed as the osmotic effects of extravasated blood recruit additional fluid and worsen localized swelling. Approximately 40% of hemorrhagic stroke victims have demonstrable hematoma enlargement over just 2 to 3 hours, a finding associated with a much higher risk of death. If hemorrhage ruptures into the ventricular system, obstructive hydrocephalus can occur, often provoking a slowly progressive downhill course. There are three classical clinical presentations of hemorrhagic stroke: (1) hemiplegia, sometimes with hemisensory impairment, when the thalamus or basal ganglia are involved; (2) sudden-onset quadraparesis, pinpoint pupils, midposition eyes, and coma occur when the pons is the site of the bleed; and (3) headache, ataxia, nausea, and vomiting when bleeding occurs in the cerebellum. Seizures are more common with hemorrhagic strokes than with ischemic lesions, hence the recommendation by some experts for 1 to 2 weeks of prophylactic anticonvulsant therapy. Virtually all hemorrhagic strokes are easily recognized on CT scan. MRI is an equally effective diagnostic tool.

Treatment of intracranial hemorrhage includes reversal of therapeutic anticoagulation, correction of endogenous coagulopathy, and blood pressure control (Fig. 34-8). Heparin may be reversed with protamine and warfarin effect reversed with plasma, vitamin K, and prothrombin complex concentrates. If depressed, platelet counts should be raised to at least 100,000/mm³.

<table>
<thead>
<tr>
<th>Site</th>
<th>Frequency</th>
<th>Clinical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putamen</td>
<td>35%</td>
<td>Contralateral hemiparesis, hemisensory loss, dysphagia, or neglect</td>
</tr>
<tr>
<td>Thalamus</td>
<td>10%</td>
<td>Similar to putamen bleed, plus forced downward gaze, upgaze palsy, unreactive pupils</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>5%</td>
<td>Confusion, memory loss, hemiparesis, gaze paresis, intraventricular blood, and hydrocephalus common</td>
</tr>
<tr>
<td>Lobar bleed</td>
<td>30%</td>
<td>Variable findings depending on location</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>15%</td>
<td>Headache, vomiting, gait ataxia, nystagmus, cranial nerve palsies</td>
</tr>
<tr>
<td>Pons</td>
<td>5%</td>
<td>Quadriplegia, pinpoint pupils, gaze palsies, ataxia, sensorimotor loss</td>
</tr>
</tbody>
</table>

Table 34-8: Site, relative frequency, and clinical characteristics of hemorrhagic stroke.
Although hypertension is a recognized risk factor in nontraumatic intracranial hemorrhage, insufficient data are available to confidently inform practice. Recent results suggest that rapid lowering of blood pressure will improve functional outcomes even though the rates of death and severe disability appear little changed. Reduction in hematoma enlargement, the presumed mechanism of improvement of rapid lowering by blood pressure, was not found.

As one of the few surgically amenable neurologic problems, cerebellar hemorrhage should be quickly recognized, radiographically confirmed, and corrected by evacuation when feasible. CT scan is the best technique to select candidates who might benefit from clot evacuation. Evacuation is generally reserved for patients with posterior fossa hemorrhage greater than 3 cm in diameter and those with brainstem compression, rupture of blood into the third ventricle, or hydrocephalus. In contrast to benefits from evacuating cerebellar hemorrhage, a large randomized trial of decompressive surgery for supratentorial hemorrhage did not
demonstrate improved outcomes. Intraventricular hemorrhage is a marker of poor outcome and can be delayed after initial neurologic presentation.

**Subarachnoid Hemorrhage (SAH)**

Subarachnoid hemorrhage (SAH) is a syndrome in which headache, nausea, vomiting, confusion, or coma is typical, but paralysis is rarely seen. Although the headache may not be described by the classic phrase: “the worst of my life,” patients often identify the headache of SAH as a unique event. Noncontrast CT typically allows rapid diagnosis while lumbar puncture also demonstrates characteristic changes of bleeding into the CSF (Fig. 34-9). Early mortality rates from SAH approach 50%, with many patients experiencing recurrent bleeding before definitive vascular repair. Thus, the trend has been to move to earlier diagnosis and repair of amenable lesions (Fig. 34-10). The traditional approach using delayed open “clipping” has evolved to earlier placement of coils or other embolic material in the aneurysm using an endovascular approach. Both endovascular and extravascular approaches appear to be equally effective for most aneurysms, but some widemouthed aneurysms are not amenable to an endovascular approach. In addition, aneurysms of the posterior cerebral and basilar arteries are difficult to access by open craniotomy.
FIGURE 34-9. Classic CT featuring rupture of aneurysm at skull base (arrow), circle of Willis, and resulting subarachnoid hemorrhage (SAH).

A second major problem occurring in about 20% of SAH patients is vasospasm. Vasospasm usually manifests as a global decline in neurologic function, beginning 3 to 5 days after the bleed with peak effect at 7 to 14 days. Although the pathophysiology of vasospasm continues to be debated, two lines of therapy appear beneficial: use of the calcium channel blocker, nimodipine, and use of induced hypertension, hemodilution, and hypervolemia, the so-called triple H therapy. Nimodipine, 60 mg every 6 hours, has been shown to decrease the risk of vasospasm after SAH but can lead to detrimental hypotension. Induced hypertension, hemodilution, and hypervolemia has few high-quality studies to support its use; however, existing data suggest benefit and it appears to be of low risk and cost. Many centers use some version of this triple H strategy. In theory, the therapy lowers blood viscosity while maintaining perfusion pressure. Likewise, although anticonvulsants are commonly administered after SAH, there are limited data to support the practice.

Complications

DVT, decubitus ulcer formation, and gastric ulceration are all very common in stroke victims. Perhaps the largest overall gains in survival of stroke patients can be achieved by preventing death from thromboembolism. By one estimate, more than one third of stroke victims develop DVT in the absence of effective prophylaxis. Hence, early institution of pharmacological prophylaxis (in patients at low risk for anticoagulation-related complications) or venous compression devices may be one of the most efficacious treatments for stroke victims. (In patients with ischemic strokes LWMH has been shown to be superior to twice-daily unfractionated heparin [UFH] with respect to effectiveness and has comparable bleeding risk.) Similarly, because gastric stress ulceration is common, early enteral feeding or proton pump inhibitor (or histamine blocker) treatment is prudent. Careful use of positioning, padding, turning, and therapeutic beds can prevent the devastating complication of skin breakdown and joint contractures. These seemingly mundane but important issues of supportive care are covered in detail in Chapter 18.
Hydrocephalus is an uncommon complication for most forms of stroke, but is far from rare in patients sustaining hemorrhagic infarction of the caudate or posterior fossa or SAH. Bleeding into the caudate nucleus ruptures into the ventricular system with considerable frequency, often resulting in a waning level of consciousness and hydrocephalus on CT scanning.

Respiratory complications of stroke, including aspiration pneumonitis and bacterial pneumonia, are extremely common and are responsible for most episodes of poststroke fever. The risk of aspiration is increased in patients fed using a “bolus” into the stomach rather than continuous infusion technique through the small bowel. Feeding patients maintained in a less than 30-degree head-up position also appears to be a risk factor for aspiration and pneumonia.

**INCREDSE INTRACRANIAL PRESSURE**

**Mechanisms**

Three tissues occupy the skull: brain substance, CSF, and blood. None is readily compressible. Therefore, swelling of the brain substance, intracranial hematoma, or blockage of the normal venous or CSF outflow leads to increased ICP. Elevated

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* FIGURE 34-10. Acute management of nontraumatic subarachnoid hemorrhage (SAH). LOC, loss of consciousness.
ICP is mitigated by the movement of one of the “liquid” components (blood or CSF) out of the cranium. Increased ICP is itself deleterious when it compromises tissue perfusion or precipitates brain herniation.

Swelling of the brain matter happens by three common mechanisms. Vasogenic edema occurs when the blood-brain barrier is disrupted by trauma or high intravascular pressures (e.g., malignant hypertension). Subsequent leak of serum proteins and water leads to interstitial edema. Cytotoxic brain edema results from impairment of cellular sodium-potassium pumping mechanisms by glial cell injury. Disrupted ion pumping allows intracellular water accumulation causing edema. The most common causes are hypoxia and toxin exposure (e.g., carbon monoxide). Osmotic edema occurs when intracellular osmolality exceeds that of plasma and CSF, and water passively moves into brain cells. The gradient for water movement can be created by raising intracellular osmolarity or reducing plasma tonicity. For example, rapid intravenous or enteral administration of large volumes of hypotonic fluid (e.g., acute water intoxication) can cause brain swelling in a previously healthy person. Another example occurs when neurons have increased intracellular tonicity because of accumulated glucose (DKA), uremic toxins (renal failure), or idiogenic osmoles (hepatic failure). In each case, treatments that rapidly reduce plasma osmolality (e.g., insulin, highflow dialysis) can cause abrupt cerebral edema.

Bleeding into the cranial vault is especially problematic for intracranial hemodynamics. Not only does the bleeding increase ICP by mass effect, but it also limits CSF absorption at the subarachnoid villi and increases CSF osmotic pressure because of red cell lysis. The swelling of injured tissue typically peaks within 72 hours of injury. ICP, however, can remain elevated for weeks if there has been significant intracerebral or intraventricular bleeding.

Cerebral Hemodynamics

The pressure perfusing the brain (CPP) is the difference between MAP and either the ICP or the pressure within the cerebral veins (whichever is greater). ICP is normally quite low (<5 mm Hg) but often reaches critically high levels (20 to 40 mm Hg) in the head-injured patient. CPP normally exceeds 60 mm Hg. Neural dysfunction predictably occurs when CPP is less than 40 mm Hg, and neuronal death occurs at CPP less than 20 mm Hg. ICP should be kept low enough to maintain cerebral perfusion and prevent cerebral herniation. Thus, the goal should be to optimize the CPP gradient by lowering ICP and raising MAP if necessary. Although an absolute target for MAP cannot be declared, maintaining MAP above 90 mm Hg will ensure an adequate CPP even as ICP approaches the critical 20 mm Hg value.

In health, cerebral autoregulatory mechanisms sensitive to arterial oxygen tension (PaO$_2$), arterial carbon dioxide tension (PaCO$_2$), and blood pressure continuously adjust cerebrovascular resistance to maintain perfusion in proportion to metabolic need and changing perfusion pressure. Arterial blood gases, cerebral metabolism, and the components of perfusion pressure (blood pressure, ICP) deserve attention in brain-injured patients because the autoregulatory mechanisms of injured tissue are impaired. In this setting, tissue perfusion directly parallels CPP and perfusion adequacy is directly influenced by cerebral metabolism.

Intracranial Pressure Monitoring

There are three reasons to insert an ICP monitor: (1) to detect life-threatening intracranial hypertension, (2) to assess the effects of therapy aimed at reducing ICP, and (3) therapeutic drainage of spinal fluid. ICP monitoring should also be considered for the patient with head injury in settings where physical examination is not available or reliable, such as general anesthesia (see below). Mean ICP of a supine patient is normally less than 10 mm Hg, and the ICP waveform normally undulates gently in time with the cardiac cycle. Extreme fluctuations of the ICP waveform (>10 mm Hg) suggest a position near the critical inflexion point of the cranial pressure-volume curve, particularly when the contour shows a high “second peak” corresponding to the arterial pulse. Elevations of ICP to 15 to 20 mm Hg compress capillary beds and
compromise the microcirculation. At levels of 30 to 35 mm Hg, venous drainage is impeded and edema develops even in uninjured tissue. This level of intracranial hypertension produces a vicious cycle in which impeded venous drainage leads to accumulating edema and further ICP elevations. Even when autoregulatory mechanisms are intact, cerebral perfusion cannot be maintained if ICP rises to within 40 to 50 mm Hg of the MAP. When ICP reaches MAP, all perfusion stops and the brain dies.

Of the three components contained within the fixed cranial volume, only the volumes of CSF and blood may be changed (unless the skull is opened and the brain is removed or made less edematous). Starting from normal levels, ICP shows little response to increases of intracranial volume until a critical inflexion point is reached. Thereafter, small increments in volume dramatically boost ICP, risking sudden deterioration (Fig. 34-11). Direct ICP monitoring is important because changes in other clinical indices—reflexes, blood pressure, and heart rate—usually occur too late to avert disaster. Bradycardia, with respiratory depression and hypertension, the Cushing reflex, reflects a critical rise in ICP.

**Specific Indications for ICP Monitoring**

**Closed Head Injury**

Although the benefits of ICP monitoring are not supported by rigorous clinical trials, it remains a common practice in treating the head-injured patient. It is not practical or necessary to monitor ICP in all such individuals, but three groups of trauma patients appear to derive benefit: (1) those with GCS 3 to 8 and an abnormal CT scan at admission, (2) patients with normal CT scans at admission but who present with hypotension (systolic pressure <90 mm Hg) or posturing, and (3) head-injured patients older than 40 years of age. A normal CT scan of the head accurately predicts normal ICP in more than 80% of cases, whereas ICP is elevated in about 50% of patients when a significant lesion is observed on head CT. Midline shift of more than 7 mm or blood in the lateral ventricles is especially worrisome. Head trauma patients with GCS scores less than 7 frequently have an increased ICP, as do patients with decorticate/decerebrate posturing or abnormal evoked potential testing. Abnormal eye or pupil movements are unreliable guides to increased ICP. Repeat head CT should be performed 6 to 24 hours after injury to assess the progress of wounds and to evaluate the degree of intracranial hypertension.
**Reye Syndrome and Fulminant Hepatic Failure**

Increased ICP from cytotoxic edema is a major cause of death in Reye syndrome. Mortality is high without prompt diagnosis and treatment. Therapeutic reductions in ICP may reduce mortality to 20% or less, with survivors experiencing few sequelae. Therefore, ICP monitoring is indicated in patients with Reye syndrome and GCS scores less than 7. The pathogenesis of increased ICP in hepatic failure of other etiologies is less certain but is probably a combination of cytotoxic osmolar impairment. ICP elevations occur commonly among patients with acute hepatic failure but rarely found among patients with chronic end-stage cirrhosis. Even though ICP monitoring is commonly performed in acute hepatic failure, at present, there is little evidence to suggest it reduces mortality.

**Brain Tumors**

ICP monitoring is rarely necessary in patients with chronic supratentorial lesions. However, ventriculostomy may be useful preoperatively to allow reduction in the CSF volume of patients with large infratentorial lesions. In patients with large brain tumors or extensive edema on CT scanning, ICP monitoring may help guide therapy.
**Contraindications to Monitoring**

Coagulopathy (platelet count <50 to 100,000/mm$^3$ or prothrombin time [PT], INR or activated partial thromboplastin time [aPTT] values >2 times normal control) is generally regarded as a contraindication to ICP monitor placement. Among patients with acute hepatic failure, coagulation disorders are often corrected with fresh frozen plasma, vitamin K, and/or platelet transfusions before ICP placement. Isolated elevations of fibrin degradation products (FDPs) should not contraindicate catheter placement; FDP levels may be increased by brain trauma alone.

**Hardware and Devices**

**Intraventricular Catheters**

Ventricular catheters may be inserted under local anesthesia at the bedside, typically through a burr hole in the skull on the “nondominant” side just anterior to the sagittal suture. Because intraventricular catheters provide continuous, reliable data and allow therapeutic removal of CSF, they are the preferred method of ICP monitoring by many clinicians. Unfortunately, ventriculostomy presents several problems. Perhaps foremost, because bleeding may accompany insertion, uncorrected coagulopathy contraindicates placement. There may also be technical difficulty encountered placing the catheter into a lateral ventricle compressed by extensive edema or mass. After insertion, the CSF invariably shows evidence of catheter irritation (mild elevations of protein and leukocyte count) making laboratory evaluation of the fluid difficult. In addition, infection is a potential complication after ventriculostomy and relates to duration of monitoring and technique of catheter placement and maintenance.

**Epidural Transducers**

Although epidural transducers present a lower risk of infection than ventricular catheters, they are technically more difficult to insert. Epidural catheters use fiberoptic or mechanical transducer membranes precisely juxtaposed to the dura. Past problems with calibration drift plaguing these devices have now largely been surmounted. The major drawback to the use of epidural transducers is the inability to remove CSF.

**Subarachnoid Screws/Bolts**

The subarachnoid screw is a hollow bolt inserted into the subarachnoid space through a burr hole (usually placed in the frontoparietal suture). During placement, the dura is opened and the device is inserted onto the brain surface. Problems with the subarachnoid screw include infection and the potential for seriously underestimating ICP if not placed on the side of an existing mass lesion. Brain herniation into the device is the most common cause for technical failure. Problems with damping and clotting are sufficiently frequent that regular flushing is mandatory. Such flushing, however, exposes patients to an increased risk of herniation and infection. Finally, these devices are frequently dislodged, even with meticulous care.

**Problems with ICP Monitoring**

Metallic monitoring devices preclude MRI imaging and produce artifacts on CT scans that can obscure important information. Infection occurs in 2% to 5% of patients who undergo ICP monitoring. Infection risk increases with the “depth of insertion” (ventricular catheters are highest), duration of monitoring, frequent device flushing, and use of an open drainage systems. Unfortunately, definitions and rates of infection vary widely. *Staphylococcus epidermidis* is a common infecting organism. As with any monitoring technique, poor-quality data may lead to inappropriate therapy. The intraventricular catheter gives the most consistent data, whereas the subarachnoid screw is less reliable but carries...
Reducing Intracranial Pressure

Lowering Jugular Venous Pressure

The goal of reducing ICP is to maintain cerebral blood flow by keeping CPP greater than 60 mm Hg. Because the ICP cannot be lower than the downstream venous pressure (CVP), patient positioning is important. Neck flexion, head turning, and tracheostomy ties impeding venous drainage should be avoided. Raising the head to at least 30 degrees virtually assures CVP will be less than ICP. Increases in CVP related to supine or prone positioning, straining, retching, and coughing should be minimized. Likewise, seizures should be prevented. Special caution should be taken during ventilation using positive end-expiratory pressure (PEEP). By raising intrathoracic pressure and decreasing venous return, high levels of PEEP have the potential to simultaneously reduce MAP and raise ICP. However, judicious use of PEEP is not contraindicated, especially because the ICP of trauma patients often exceeds the PEEP-affected CVP.

Sedation and Analgesia

A struggling, agitated patient may acutely elevate CVP, thereby raising ICP. Even comatose patients can experience increased ICP in response to noxious stimuli; therefore, appropriate sedation and analgesia are indicated. Narcotics represent a good analgesic choice because they have some sedative effect, they reduce pain, and their antitussive action can avoid transient detrimental increases in ICP. Propofol is the sedative of choice for most patients because it has a rapid onset and offset of action, is readily titrated, lowers ICP, and has anticonvulsant properties. Benzodiazepine sedatives also provide the anticonvulsant benefit. Regardless of the sedative or analgesics chosen, it is important to administer doses that do not result in hypotension. In extreme cases, neuromuscular blocking drugs must be added to deep sedation and analgesia to avoid intracranial hypertension.

Osmotic Agents

Mannitol and hypertonic saline work by establishing an osmotic gradient between the CSF and blood, thereby promoting fluid transfer from brain cells and CSF to the circulation. Increasing the blood osmolality by 10 mOsm/L has a net effect of acutely removing about 100 mL of intracellular water from the brain. The use of osmotic agents is not standardized because the optimal choice of agent, dose, and frequency of administration has not been determined in clinical trials. Mannitol given in boluses of 0.25 to 1 g/kg every 4 to 6 hours is the traditional choice, but hypertonic saline is now perhaps more popular. In doses that produce a serum osmolarity greater than 320 mOsm/dL, all osmotic agents slowly penetrate the blood-brain barrier, gradually counterbalancing their initial therapeutic effect. Even when serum osmolarity is maintained below this threshold, osmotic agents have a tendency to leak into the most severely damaged areas of the brain. Furthermore, when given rapidly, large doses of osmotic agents may expand the circulating volume, elevate ICP, and produce hemodilution. Simultaneous administration of loop diuretics can often offset this unwanted intravascular volume expanding effect. By dehydrating red blood cells, osmotic agents can also result in a decrease in hematocrit with a preserved or elevated hemoglobin concentration (pseudoanemia). Excessive diuresis, however, depletes intravascular and/or intracellular volume. Rebound intracranial hypertension is a significant problem that may be seen after discontinuation of any osmotic agent. Doses of mannitol that produce high osmolarity (>340 mOsm/dL) should be avoided because they may impair renal tubular function.
Hyperventilation
Hyperventilation rapidly but temporarily lowers ICP. Acute reduction of PaCO$_2$ raises tissue pH, causing cerebral vasoconstriction in normally responsive cerebral vessels (Fig. 34-12). Within wide limits, reduced flow through normal brain tissue is well tolerated. As flow and vascular volume fall, ICP declines, thereby boosting CPP. By contrast, flow to the injured, poorly autoregulated brain actually improves because flow through injured areas is CPP dependent. Although brief moderate hyperventilation tends to reduce ICP, improve CPP, and improve flow to damaged tissue, extreme (PaCO$_2$ < 25 mm Hg) or prolonged hyperventilation offsets this potentially beneficial action by causing excessive vasoconstriction and global reduction of perfusion. (Reducing PaCO$_2$ is effective for less than 24 hours during which renal compensation gradually restores acidbase status and eventually negates its effects.) For years, it has been known that prolonged hyperventilation is associated with worse neurologic outcomes than normocapnia. Thus, hyperventilation is best viewed as a stopgap measure to lower ICP for minutes to hours as other measures (i.e., osmotic diuretics, ventricular drainage, or craniotomy) are undertaken to lower ICP definitively. Although the therapeutic benefits of hyperventilation are debated, it is clear that hypoventilation should be avoided; increased blood flow and vascular volume can drive ICP quickly to life-threatening levels. Associated hypoxemia accentuates the risk, because like hypercapnia, hypoxemia is a cerebral vasodilator of brain tissue. If instituted, hyperventilation should be terminated in stages (over 24 to 48 hours) to avoid causing rebound increases in ICP and brain ischemia.

![Relative CBF vs PaCO$_2$ and PaO$_2$](image)

**FIGURE 34-12. Effect of arterial gas tensions on cerebral blood flow (CBF) in normal brain tissue (autoregulation intact).** Whereas reductions of PaCO$_2$ lower CBF (and cerebral volume) in more or less linear fashion over the physiologic range, reductions in PaO$_2$ have an opposite effect that manifests only when the O$_2$ content of hemoglobin falls (PaO$_2$ < 60 mm Hg). Injured tissue may lose this ability to autoregulate flow in response to blood gas (or blood pressure) changes.

Corticosteroids
Corticosteroids reduce cerebral edema associated with tumors, but there is no evidence that they benefit patients with cerebral edema from head trauma.
or metabolic encephalopathy. Moreover, corticosteroids increase the risks of nosocomial infection and hyperglycemia. Steroids may, however, benefit the outcome of some forms of acute spinal injury (see below).

**Ventriculostomy Drainage**

The removal of CSF may acutely lower ICP, especially when the system is poised on the steep portion of the ICP-volume curve. Because CSF production is a continuous process, the effects of intermittent CSF removal are transient (<2 hours). Equipment for continuously venting the CSF to maintain ICP at or below a given hydrostatic level are effective in reducing ICP but increase the risk of infection. Nonetheless, CSF drainage makes consummate sense in the setting of aqueductal blockage (e.g., by clotted blood in the fourth ventricle). Here, venting CSF output until clot lysis occurs (approx. 5 to 7 days) may prove lifesaving. By contrast, withdrawal of spinal fluid from the lumbar region may precipitate brain herniation by increasing the pressure gradient across the tentorium.

**Surgery**

A direct attack on the cause of increased ICP may be indicated in such conditions as obstructive hydrocephalus (improved by shunting), tumor, or large but focal hemorrhage (particularly into the cerebellum). Similarly, prompt evacuation of a large subdural hematoma may be lifesaving. Removal of a cranial flap (decompressive craniectomy) may be an effective maneuver to allow edematous brain room to expand outside the skull.

**Therapy to Minimize Cerebral Oxygen Requirements**

Fever and agitation greatly increase cerebral metabolic requirements and should be prevented. Nonsteroidal anti-inflammatory agents like ibuprofen are more effective than acetaminophen for fever reduction. It is a serious mistake to use methods of temperature control (e.g., cooling blankets) that induce shivering, a maneuver that dramatically increases oxygen consumption. Even if not shivering, conscious patients are made much more uncomfortable, thereby increasing cerebral metabolism and raising intrathoracic and intracerebral pressures. Although neuromuscular blocking drugs will effectively prevent shivering, they obliterate physical examination findings and predispose to a host of other complications including skin breakdown and myopathy.

High-dose barbiturates decrease cerebral metabolism and blood flow and therefore have been hypothesized to have a neuroprotective effect. Barbiturate therapy for head injury is typically a lastditch effort and one that probably mandates ICP monitoring. Pentobarbital is the drug most commonly used in loading doses of 10 mg/kg over 30 to 60 minutes, followed by infusions of 1 mg/kg/h. Barbiturates so often induce hypotension that volume expansion and vasopressor use are frequently necessary. These drugs also obliterate both the EEG signals and the clinical parameters used for neurologic assessment. As an alternative to barbiturates, benzodiazepines and propofol can be used to reduce cerebral oxygen consumption. When sedative drugs are used to control intracranial hypertension, they are typically continued for 24 to 48 hours after ICP has normalized and then are slowly tapered.

**HEAD TRAUMA**

**Pathophysiology**

High-speed motor vehicle accidents and falls account for the vast majority of serious head and neck injuries. Head trauma from these incidents injures neural tissue by primary (direct brain tissue injury) or secondary mechanisms (hypoperfusion, vascular disruption, and increased ICP). The concussive forces produced by a blow to the head are usually greatest at the point of application and diametrically across the skull from the site of the blow (contrecoup injury). Bony prominences on the base of the skull also commonly cause injury, particularly to the inferior surfaces of the frontal and temporal lobes. Primary diffuse brain injury is characterized by immediate loss of consciousness as shearing forces disrupt RAS function.
Secondary brain injury is characterized by hypoxia, hypoperfusion, or increased ICP, resulting from tissue edema, hydrocephalus, or mass lesions (fluid/blood accumulations, epidural or subdural hematomas, intracerebral hemorrhage, abscess, or empyema). Secondary mechanisms are responsible for approximately half the deaths that follow head injury. Therefore, optimal management of these consequences could theoretically reduce mortality by as much as 50%. Global ischemia, hypoxia, and vascular disruption also increase the severity of cerebral injury. The clinical hallmark of secondary injury is a progressive decline in level of consciousness after the initial injury.

Initial Management

Nearly half of all head-injured patients have other accompanying life-threatening medical problems (i.e., hypotension, hypoventilation, hypoxemia, or hypercarbia) on arrival at the hospital. In general, there is no head injury sufficiently severe to cause hypotension unless the patient is near death. Therefore, other sources of bleeding must be considered. Although often visually impressive, hemorrhage from scalp wounds is rarely life threatening and is almost always easily controlled by direct pressure or rapid mechanical closure. Potentially lethal thoracic or abdominal injuries must be sought and corrected simultaneously by a multidisciplinary team.

An unstable airway, ineffective ventilation, and reduced oxygen delivery resulting from hypovolemia or anemia must be promptly corrected. The initial priority is airway management, particularly if the GCS is 8 or less. If direct laryngoscopy is chosen for airway control, “in-line” traction should be used to stabilize the cervical spine without neck hyperextension. Fiberoptic intubation and intubation facilitated by video laryngoscopy are useful options to avoid manipulation of a potentially unstable spine. Basilar skull fractures or facial fractures usually contraindicate nasotracheal intubation or placement of nasogastric tubes. Rapid sequence intubation is preferred for most head trauma victims because they often have full stomachs, predisposing to aspiration. Supplemental oxygen and mechanical ventilation counter respiratory acidosis and hypoxemia. PEEP should be used judiciously to reverse refractory hypoxemia, recognizing that PEEP raises the outflow pressure of the cerebral veins and potentially increases the formation of cerebral edema. Hypotension should be avoided. (See additional detail below.) MAP should be restored to at least 60 mm Hg with isotonic fluids to replace intravascular volume losses before vasopressors are used. A central venous catheter will be required to administer vasoactive drugs. Although suboptimal when used alone, a typical goal of invasive hemodynamic monitoring is a CVP of 8 to 12 mm Hg. Ultrasound can be a valued adjunct in assessing intravascular volume adequacy. The optimal goal in this setting is unknown and is best determined by overall clinical response of the patient. Norepinephrine is preferred over dopamine if a vasopressor is needed to increase perfusion pressure. Positioning the patient with the head elevated 30 degree or more will help limit the formation of cerebral edema, and this inclination does not impair CPP. Care should be taken to prevent flexion or rotation of the neck, which can exacerbate spinal injury and obstruct jugular venous outflow, in turn lowering CPP. Following initial stabilization, complete physical and neurologic exams and CT imaging of the head and neck should be performed (Fig. 34-13).

Avoidance of secondary brain injury is essential to improve outcome in the head-injured patient. A physiologic goal set for TBI care is given in Table 34-9. Any episode with SaO$_2$ less than 90% or arterial blood pressure less than 90 mm Hg is associated with incremental reduction in the likelihood of a good outcome. GCS and pupillary exam will guide initial management. Evidence of intracranial mass effect such as unequal pupils, asymmetric motor exam, and decline in level of consciousness should indicate that the patient is at significant risk for intracranial hypertension. In general, the cause of increased ICP is on the side of a dilated pupil.

Several strategies are routinely available to manage patients with clinical evidence of elevation in ICP. Hyperventilation acts by reducing PaCO$_2$ and causing cerebral vasoconstriction. However, aggressive and
prolonged hyperventilation may promote cerebral ischemia in the already injured brain by causing cerebral vasoconstriction and reduced cerebral perfusion. This is particularly true if the PaCO$_2$ falls below 30 mm Hg. However, hypercarbia (PaCO$_2$ > 45 mm Hg) will promote vasodilation and increase ICP. Hypercarbia, thus, should be avoided. Hyperventilation should only be used in moderation and for as short a period as possible. In general, maintain the PaCO$_2$ at 35 mm Hg.

Mannitol and hypertonic saline may also be used to reduce elevated ICP. The preparation of mannitol most commonly used is a 20% solution. Mannitol should not be given to patients with hypotension because mannitol does not lower ICP in hypovolemia and is a potent osmotic diuretic. Hypertonic saline is also used to reduce elevated ICP. Concentrations of 3% to greater than 20% are used, and this may be the preferable agent to use in patients with hypotension as hypertonic saline does not act as a diuretic. Contemporary literature demonstrates increasing support for hypertonic saline over mannitol for management of acutely elevated ICP.

FIGURE 34-13. Classic CT imaging presentations in TBI. (Letters A-F represent individual patients).
**Physical Examination**

After assuring adequacy of the airway, oxygenation, and blood pressure, a rapid neurologic examination should be conducted, including assessment of the GCS (see Table 34-4). The GCS is potentially useful as a prognostic tool and to help gauge the need for invasive ICP monitoring. Neurologic examination of head-injured patients is often difficult when complicated by coma and the ingestion of ethanol or other intoxicants. The examiner of head trauma patients should look for evidence of penetrating wounds, spinal cord damage, and depressed or basilar skull fractures (evidenced by blood behind the tympanic membrane, CSF rhinorrhea, raccoon eyes, or discoloration behind the ears—the Battle sign). Papilledema is a particularly useful finding in the head trauma patient, indicating an elevated ICP.

**Radiographic Evaluation**

Practically speaking, almost all patients with a history of high-speed collision, fall, loss of consciousness, or strong blow to the head will be brain scanned (Fig. 34-13). It is generally agreed that immediate CT scanning is indicated for patients with (1) GCS scores less than 15, (2) focal neurologic deficits, (3) evidence of skull fractures, (4) a deteriorating level of consciousness, and (5) planned immediate surgery. For most patients, a noncontrast study is sufficient to detect significant injuries. At a minimum, neurosurgical consultation should be obtained for all patients with intracranial hematoma and/or skull fracture. Any patient suspected of significant head injury should undergo precautions for spinal injury and radiographic evaluation of the spine, which is often performed at the time of initial head CT. In general, patients with extra-axial hematoma (extra- or subdural >1 cm in thickness) and those with intraparenchymal hematoma greater than 3 cm in diameter or greater than 5-mm midline shift associated with a hematoma are considered surgical problems.

<table>
<thead>
<tr>
<th>Table 34-9. Physiologic Targets for TBI Care</th>
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<tbody>
<tr>
<td>- Pulse oximetry SaO₂ &gt; 90%</td>
</tr>
<tr>
<td>- PaCO₂ 35-45 mm Hg</td>
</tr>
<tr>
<td>- SBP &gt; 90 mm Hg</td>
</tr>
<tr>
<td>- pH 7.35-7.45</td>
</tr>
<tr>
<td>- ICP &lt; 20 mm Hg</td>
</tr>
<tr>
<td>- PbtO₂ &gt; 15 mm Hg</td>
</tr>
<tr>
<td>- CPP 50-70 mm Hg (45-60 mm Hg in children)</td>
</tr>
<tr>
<td>- Temperature 36.0°C-38.3°C</td>
</tr>
<tr>
<td>- Glucose 80-180 mg/dL</td>
</tr>
<tr>
<td>- Serum sodium 135-145 mmol/L</td>
</tr>
<tr>
<td>- INR &lt; 1.4</td>
</tr>
<tr>
<td>- Platelets &gt; 100 x 10³/mm³</td>
</tr>
<tr>
<td>- Hgb &gt; 7 g/dL</td>
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</tbody>
</table>

ICP, intracranial pressure; PbtO₂, oxygen tension in brain tissue; SaO₂, hemoglobin oxygen saturation; SBP, systolic blood pressure.
Cranial Disruption

Linear skull fractures of the cranial vault are more common than basilar skull fractures and imply that a substantial blow has been sustained. Fractures of the vault are of particular significance when they traverse the course of the middle meningeal artery, suggesting the possibility of epidural hematoma. Depressed skull fractures or penetrating injuries produce damage as the inner table of the skull is driven inward, injuring vessels and the brain surface. Such injuries usually result from the impact of small, high-velocity objects and carry a high risk of bacterial infection. Injuries causing skull fractures are often associated with intracranial bleeding.

Basilar skull fractures are accompanied by unique associated injuries, but also indicate high severity impact. Basilar fractures are seldom seen on plain radiographs and can be missed even by CT. CSF leakage into the sinuses is common when the floor of the middle cranial fossa is fractured. By contrast, CSF leak into the external auditory canals from temporal bone fractures is less common. Nasal bleeding occurs commonly when the floor of the anterior fossa is damaged. In such cases, transnasal tubes must not be inserted blindly because of the possibility of passage through the base of the skull into the brain. (The same precaution applies to stylet-stiffened small-bore feeding tubes.) Nasal packing should be avoided in patients with CSF leakage because of the increased risk of meningitis. Febrile patients with basilar skull fractures must be treated as if meningitis were suspected, employing LP and the early institution of antibiotics. Although recurrent meningitis is a feared complication of basilar skull fracture, CSF leaks seldom need surgical closure (<1% of all cases).

Injury to Brain Tissue

Cerebral contusion from rapid deceleration is the most common mechanism of brain injury. Subsequent cerebral edema and increased ICP may exacerbate damage. One form of this injury, brainstem contusion, is characterized by intermittent agitation, disordered autonomic regulation, and episodic hyperthermia. Mass lesions and the effects of cerebral edema produce secondary brain injury by displacing cerebral contents across anatomic boundaries or by globally decreasing perfusion (Fig. 34-14). Translocation of brain tissue may occur through bony defects or by subfalcial, transtentorial, or foraminal herniation.

Intracranial Hematoma

The risk of the main types of trauma-induced intracranial bleeding (epidural hematoma, subdural hematoma, intracerebral hematoma, and SAH) can be estimated by physical examination and knowledge of the presence or absence of a skull fracture. Presence of a skull fracture and a low GCS predict a high likelihood of intracranial hematoma. For example, patients with normal GCS scores (i.e., 15) and no skull fractures have a low risk of intracranial hematoma, whereas patients with GCS scores less than 8 with skull fractures have a much higher risk. It is vital to diagnose and surgically correct intracranial hematomas as rapidly as possible. Older data indicate that delaying repair for a little as 4 hours can triple the mortality rate (30% to 90%). Adequate management of CPP, glucose, and blood pressure is instrumental.
FIGURE 34-14. Potential sites of brain herniation: (1) transcranial, (2) subfalcial, (3) transtentorial, and (4) foraminal.

Epidural hematoma occurs in a minority of patients (about 10%) with severe closed head injury and usually presents as a rapidly expanding clot in a patient with a linear skull fracture. (The accumulating blood is located between the dura and the skull.) Vascular disruption usually occurs where the fracture crosses the course of the middle meningeal artery, the dural sinuses, or the foramen magnum. Most epidural hematomas occur over the temporal lobes where the skull is thin and highly vascular. An enlarging epidural hematoma most commonly results in medial compression of the temporal lobe. Clinically, this process presents as loss of consciousness, contralateral hemiparesis, and a third nerve palsy with ipsilateral pupillary dilation. Not all patients have a classic “lucid interval.” When severe, death eventually occurs as the midbrain is compressed against the tentorium. Because epidural hematoma has an associated mortality approaching 50%, it usually requires urgent neurosurgical intervention. Therefore, any trauma patient who demonstrates a linear skull fracture or who loses consciousness (even transiently) probably should be admitted to the hospital for observation.

Acute subdural hematoma, blood accumulation between the brain and the dura, is an expanding mass that
results from cortical contusion and laceration of a meningeal vessel. It is more common than an epidural hematoma, occurring in about 20% of patients with serious closed head injury. Subdural hematoma is associated with high mortality and as a rule requires urgent surgical attention. In contrast to epidural hematoma, which usually requires substantial force, subacute or chronic subdural hematoma may occur as the result of a seemingly trivial injury to enlarged dural venous sinuses. Subdural hematoma most frequently occurs in the elderly because cortical atrophy stretches the subdural veins, predisposing them to injury. A typical presentation of a subacute or chronic subdural hematoma is slowly progressive confusion, somnolence, and headache that lead eventually to hemiplegia. Anticoagulants greatly increase the risk of posttraumatic hematoma formation.

Intracerebral hematoma develops in about 40% of all cases of severe brain injury (Fig. 34-3). The clinical presentation of intracerebral hematoma depends on the location of the bleeding. The CT scan is useful in delineating this mass, which appears initially as a dense intraparenchymal collection of blood. If an intracerebral hematoma produces mass effect, it should be surgically evacuated. Intracerebral hematoma often evolves over 12 to 24 hours; therefore, a decrease in level of consciousness, increasing headache, or focal neurologic signs should prompt a repeat scan. Intracerebral hematoma develops in about 40% of all cases of severe brain injury (Fig. 34-3). The clinical presentation of intracerebral hematoma depends on the location of the bleeding. The CT scan is useful in delineating this mass, which appears initially as a dense intraparenchymal collection of blood. If an intracerebral hematoma produces mass effect, it should be surgically evacuated. Intracerebral hematoma often evolves over 12 to 24 hours; therefore, a decrease in level of consciousness, increasing headache, or focal neurologic signs should prompt a repeat scan.

Subarachnoid hemorrhage also occurs in the setting of traumatic brain injury. Traumatic SAH results from venous tears within the subarachnoid space. Injured vessels are small and the resulting hemorrhage frequently appears as a thin diffuse hyperdensity over the cerebral convexity. The usual location of traumatic subarachnoid hemorrhage distinguishes it from SAH caused by spontaneous rupture of a cerebral aneurysm where bleeding is most prominent in the basilar cisterns and appears thicker on CT imaging. Occasionally, traumatic SAH may have a CT appearance similar to that of aneurismal SAH, and if detailed history cannot distinguish between spontaneous and traumatic SAH, imaging of the vasculature via CT angiography, MRI, or catheter angiography may be necessary. In general, no specific treatment is needed for traumatic SAH.

Complications of Head Trauma

One of the most common complications of head trauma, increased ICP, is discussed in detail above. Direct neuronal injury causes seizures with sufficient frequency that prophylactic use of an anticonvulsant (e.g., phenytoin) is prudent for the first week after injury. Direct injury to the hypothalamus or pituitary or increased ICP may disrupt the normal secretion of hypophyseal hormones. Loss of antidiuretic hormone (ADH) may cause acute diabetes insipidus (DI). Unless it is due to direct hypophyseal vascular injury, DI is usually an indicator of a poor prognosis, from prolonged increases in ICP. Such patients can produce massive volumes (>1 L/h) of dilute urine despite increasing serum osmolality. Typically, the serum sodium concentration exceeds 145 mEq/L at a time that urine specific gravity is below 1.003. Life-threatening hypovolemia and hyperosmolarity may result unless prompt treatment with hypotonic fluids and ADH is instituted. An empiric trial of aqueous vasopressin (5 units subcutaneously) is often diagnostic (see also Chapter 32). In the absence of DI, hypotension in the head-injured patient should always be assumed to be due to blood loss from an extracranial site. With the exception of adrenocorticotropic hormone (ACTH) deficiency, which may result in acute adrenal insufficiency, loss of other pituitary hormones (e.g., growth hormone, thyroid-stimulating hormone) is not an urgent problem.

Disruption of the dura by penetrating trauma or bony fracture (e.g., basilar skull fracture) may provide a pathway for the entry of microorganisms into the CSF, resulting in recurrent posttraumatic meningitis. Nosocomial sinusitis resulting from obstruction of the sinus ostia by nasal tubes and impaired drainage in the supine position affects...
10% to 15% of all headinjured patients. Serious head injury may also disrupt or block normal channels of communication of CSF. Such disruptions may cause obstructive hydrocephalus with subsequent elevations in ICP.

Erosive (stress) gastritis occurs with sufficient frequency that use of H<sub>2</sub> blockers or proton pump inhibitors is wise. Because head injury induces a hypermetabolic state, caloric requirements are elevated and nutritional supplementation is usually needed (see Chapter 16). After a brief period of posttraumatic ileus, enteral tube feeding is usually well tolerated until the patient can eat normally. Starting enteral feeding within the first 36 hours of injury may even reduce the risk of infectious complications. In patients with severe persistent neurologic deficits, consideration should be given to placement of a permanent feeding gastrostomy. This is most efficiently accomplished at the same time a permanent tracheostomy is created for long-term airway control.

Although full-blown acute respiratory distress syndrome (ARDS) may result from some combination of aspiration, chest trauma, shock, and massive transfusion, milder acute lung injury often follows head injury alone. Many hypoxemic head-injured patients have normal chest radiographs. The mechanism of hypoxemia in these patients is likely related to autonomic alterations directly induced by the trauma. Neurogenic pulmonary edema may result from head trauma, presumably because of catecholamine-induced profound and transient venoconstriction. Therapy consists of supportive care using oxygen and intubation, mechanical ventilation, and PEEP when indicated. The more mundane but frequent pulmonary complications of aspiration pneumonitis and atelectasis usually respond to standard therapy. Aspiration risk can be minimized by avoiding bolus feeding and elevating the head of the bed at least to 30 degrees. Atelectasis and “retained airway secretions” are best prevented and treated by maintaining end-expiratory lung volume, encouraging activity, providing effective suctioning, and stimulating deep breathing and coughing. These standard measures can be problematic for patients with increased ICP, because each tends to further raise the pressure. In the tenuous patient with intracranial hypertension, deep sedation and intratracheal lidocaine can be used to block increases in ICP induced by suctioning. Bronchoscopy may be employed for secretion clearance in these patients. Unfortunately, this procedure is a potent stimulus to raising ICP.

Severe head trauma causes the systemic activation of the clotting cascade, probably through the release of brain thromboplastin into the circulation.

Up to one fourth of all severely head-injured patients exhibit laboratory features of disseminated intravascular coagulation. Factor-specific therapy is rarely required, as such defects are usually self-limited. On the other hand, DVT occurs in many unprotected patients after significant head and spinal cord injury. Prophylaxis is clearly indicated; however, substantial controversy exists over the best method. Because of the risk of anticoagulation-induced or aggravated intracranial bleeding early after injury, a combination of graded compression stockings and intermittent pneumatic compression devices is usually preferred initially, but when the risk of bleeding diminishes, pharmacologic prophylaxis is clearly superior (see Chapter 23).

Decubitus ulcers are also a common problem for the head- and spine-injured patient. The best course of therapy is to prevent skin breakdown through use of padding, frequent repositioning, and promoting physical activity. Especially high-risk patients may be treated with specialized therapeutic beds. Decubitus ulcers are discussed in detail in Chapter 18.

Monitoring the Brain-Injured Patient

Careful monitoring of the neurologic exam and use of the GCS are helpful, especially in mild-to-moderate injury. Although no specific electroencephalographic (EEG) pattern defines etiology or prognosis in head trauma, the EEG is useful to monitor for seizures and document the suppression of brain activity in barbiturate-induced coma. Serial CT scans also give valuable information regarding the nature and evolution of the injury process.
However, the only way to accurately assess ICP in the seriously injured, comatose patient is to monitor it directly.

**Recovery Phase**

Recovery of consciousness following cerebral trauma may be a prolonged process, much more so than following nontraumatic coma. It is not uncommon for head trauma victims to require a year or longer to maximize their level of function. Head trauma victims are fragile, even long after the injury. Once the acute insult subsides, vigilance must be maintained to ensure that reversible factors do not impede the return to normal function. Metabolic derangements (spontaneous or iatrogenic) are sometimes responsible for persistently depressed consciousness. Hyperosmolarity, hypovolemia, and hyponatremia are frequently induced by the therapies applied in the treatment of these disorders such as diuretics, fluid restriction, and osmotic agents.

**SPINAL CORD TRAUMA**

**Epidemiology**

Roughly 12,000 new cases of spinal cord injury occur each year in the United States. Mechanisms of spinal cord injury include motor vehicle crash (42%), falls (27%), interpersonal violence (15%), and sports (8%). In over 50% of patients, injuries to the spine are isolated, whereas nearly 25% of patients have concomitant brain, chest, and/or major extremity injuries. The first peak of incidence occurs in adolescents and young adults, whereas a second peak occurs in the elderly (age >65 years). Life expectancy for a patient who sustains spinal cord injury is significantly lower than that for the general population.

Injuries to the spine tend to occur in zones of maximal mobility. Cervical spinal cord injury accounts for over 50% of traumatic spinal cord injury and is associated with much higher short- and long-term morbidity than injuries affecting the spinal cord at the thoracic or lumbar level. The most frequent injuries are incomplete tetraplegia (31%) followed by complete paraplegia (25%), complete tetraplegia (20%), and incomplete paraplegia (19%) (Fig. 34-15).

**Mechanisms**

Spinal cord injuries most frequently occur to young people and involve the region of the spine subject to the greatest motion, the cervical area. Because the mechanism of spinal cord injury is usually one of high-speed and rapid deceleration, other life-threatening traumatic injuries (intracranial, intrathoracic, or intra-abdominal) should be sought. Because they coexist so commonly, patients with spinal cord injury should be evaluated for head injury and vice versa.

Spinal cord injury is called “complete” when there is no neurologic function below the level of injury or “incomplete” when some distal function remains. Aside from interrupting its blood supply, the spinal cord is typically injured by three basic mechanisms: flexion-rotation, compression, or hyperextension. Laceration of the spinal cord is seen with penetrating trauma. Cord contusion is the feature common to all of these mechanisms. A minority of cord injuries result from primary disruption of its vascular supply. (Dissecting aortic aneurysm with or without concomitant cocaine use is probably the most common cause of vascular disruption.) Spinal cord injury should be suspected in every trauma patient with back or neck pain accompanied by sensory or motor deficits.
FIGURE 34-15. Severe distraction injury at C5, C6 level. Acute injury seen well on the sagittal CT scan. Spinal cord injury persists after fixation of the bony insult shown on the MRI view.

Flexion-rotation injury of the neck usually occurs when the neck is hyperflexed onto the trunk out of the midline axis, disrupting the posterior spinal ligament. Motor vehicle accidents are the most common cause. At a minimum, patients with flexion-rotation injury require closed reduction and traction. If radiographs demonstrate displacement of a vertebral body by greater than one half its width, instability and bilateral facet dislocation are more likely. Displacement less than one half the width of the vertebral body suggests unilateral dislocation, a less serious problem. Facet injuries are potentially unstable after reduction and many require surgery for fixation. If facets in the lumbar region become “locked,” surgery is usually necessary.

Compression injuries most commonly result from diving accidents or falls from height. In this setting, bone fragments or expanding hematoma may lead to neural damage by protruding into the spinal canal. However, these injuries are usually stable because spinal ligaments remain intact.

Hyperextension (“whiplash”) injuries in the cervical region are usually stable. These injuries occur in older patients with cervical arthritis and are frequently associated with bleeding into the spinal gray matter, producing a “central cord” syndrome.

Initial Management
All passive and active motion of the spine should be prevented in patients with suspected spinal injury. Adequate ventilation and circulation should be ensured and oxygen administered if hemoglobin saturation is below normal. Autonomic instability often occurs in the early phase, so mild hypotension is common. Judicious filling of the intravascular compartment is indicated, but because of disordered vasoregulation, it is important not to administer excessive volumes of fluid. Other measures key to the resuscitation of the trauma victim, such as airway control, venous access, and chest tube insertion, should be performed as required.

Physical Examination
Following spinal immobilization and stabilization of the airway and circulation, a detailed neurologic examination should be conducted. Complete spinal cord disruption produces loss of all sensory and motor function below the level of the injury, initially resulting in flaccid paralysis and loss of deep tendon reflexes that lasts for 2 to 7 days—the “spinal shock” phase. Incomplete cord injuries carry a better prognosis because some function is retained distal to the level of the injury. In a cooperative patient, many clinically important injuries may be diagnosed at the bedside. If the patient is able to take a spontaneous deep breath, cervical roots C2-C5 are probably intact and diaphragm function is preserved. If the patient can raise and extend the arms, C5-C7 are intact. The ability to open and close the hand assures function of C7-T1, whereas the ability to elevate the legs confirms the integrity of L2-L4. Wiggling the toes indicates that L5-S1 roots are functional. Normal anal sphincter function implies preserved function of roots S3-S5.

**Clinical Syndromes (Fig. 34-16)**

The anterior cord syndrome results from vascular compromise of the anterior spinal artery distribution and subsequent ischemic injury to the anterior two thirds of the spinal cord. Typical mechanisms are blunt trauma or ischemic injury. Patients present with loss of motor function and pain and temperature sensation below the level of the injury from involvement of the ventrally located lateral cortical spinal and spinothalamic tracts. Patients typically retain proprioception and the ability to sense vibration and deep pressure from preservation of the posterior columns of the spinal cord. The chance of clinical recovery is poor.

Traumatic central cord syndrome is associated with a contusion, ischemia, or hemorrhage in the central portions of the spinal cord due to traumatic injury sustained in the cervical or upper thoracic spine. This syndrome is characterized by weakness in the arms with burning hands and relative sparing of lower extremity function associated with variable sensory loss. Central cord syndrome results from cervical hyperextension in patients with preexisting degenerative changes and narrowing of the spinal canal. Clinically, upper extremities are more involved than lower extremities because of the more central location of the upper extremity axons within the spinal cord tracts. These patients typically walk but have more limited return of upper extremity function.
The Brown-Sequard syndrome represents an incomplete spinal cord syndrome where hemi-transection of the cord frequently occurs with penetrating injury. This syndrome is characterized by unilateral damage to the cortical spinal tract, spinothalamic tract, and dorsal columns. Clinical presentation consists of loss of ipsilateral light touch, proprioception, and motor function with contralateral loss of pain and temperature sensation.

Posterior cord syndrome is relatively rare and results from involvement of the dorsal columns with subsequent loss of proprioception and vibration with preserved motor function. These patients may experience difficulty walking due to the deficit in proprioceptive sensation.

The cauda equina syndrome represents an injury to the cauda equina with compromise of the lumbar and sacral nerve routes. These patients have lower motor neuron findings with sensory loss and motor dysfunction. Involvement of lower sacral routes may result in bladder and bowel dysfunction.
Radiographic Evaluation

After initial examination and stabilization, radiographs of the spine should be obtained. In many centers, the use of plain radiographs has now been supplanted by immediate CT scanning with MRI to evaluate ligamentous stability. Nonetheless, many spinal injuries may be seen on a single lateral view of the spine if proper technique is used. Even in cases where bone injury does not occur, ligamentous injury may cause an expanding hematoma with cord compression. Thoracic and lumbar radiographs should be obtained if there is any suspicion of injury in those locations based on patient complaints or by examination. It is important to visualize all seven cervical vertebrae because C7 is commonly injured but least commonly seen on portable radiographs. A “swimmer’s view” or traction on the patient's arms may aid visualization of C7 and T1. The alignment of the anterior and posterior aspects of each vertebral body, the alignment of the spinolaminal lines, and the contour of the spinous processes and vertebral bodies should be reviewed. The prevertebral space should be examined for evidence of widening because of hemorrhage. Open mouth views are prudent to obtain to look for odontoid fractures. Radiographs should visualize the entire spine if a fracture is found. (Up to 20% of patients have multiple levels of injury.) Even when patients have no radiographic evidence of spinal cord injury, the cervical spine should remain immobilized until the patient can cooperate with a clinical examination searching for pain with motion or tenderness to palpation.

Treatment

The use of steroids following acute traumatic cervical spinal injury is highly controversial and is both institution and practitioner specific. This practice is based on experimental work in animal models suggesting that methylprednisolone has neuroprotective effects through an anti-inflammatory mechanism. This led to a series of contradictory trials with some data indicating efficacy of high-dose methylprednisolone if given within 8 hours of injury, but subsequent data raising significant concerns about increased complications including pneumonia and gastrointestinal bleeding. Major societies addressing spinal cord injury now suggest that there is insufficient evidence to support a standard favoring methylprednisolone use. When used, a short course of high-dose methylprednisolone (30 mg/kg bolus then 5.4 mg/kg/h for 23 hours) is employed. This regimen may improve motor function. Risks include nausea and emesis.

Patients with spinal cord injury above the T4 level are at high risk for development of neurogenic shock. These individuals suffer sympathectomy that results in unopposed vagal tone, distributive shock with hypotension, and bradycardia. Hypotension in patients with neurogenic shock is usually accompanied by warm, dry skin, as opposed to the cold extremities of those who are hypovolemic from hemorrhage. Nonetheless, in patients with multiple injuries, other causes of hypotension, including hemorrhage, must also be sought, identified, and addressed. Signs of neurogenic shock may be expected to last from 1 to 3 weeks. A related clinical phenomenon, termed spinal “shock,” refers not to hypotension but to the loss of spinal reflexes below the level of injury. First-line treatment of neurogenic shock is fluid resuscitation to maintain euvoemia. Loss of sympathetic tone leads to vasodilation and the need to restore circulating blood volume.

Once euvolemia is accomplished, second-line therapies are vasopressors and/or inotropes. There is no recommended single agent but norepinephrine, with its alpha- and beta-activity, is frequently the indicated drug. Another option is the purely alpha-agonist phenylephrine, which may be safely infused through a peripheral intravenous line. Phenylephrine lacks beta-activity so it does not address bradycardia and may actually worsen bradycardia through reflex mechanisms. Phenylephrine is best used in patients with high thoracic lesions in whom
Complications

Progressive neurologic impairment is only one of the many complications of spinal cord injury. These include iatrogenic problems induced by spinal manipulation or inappropriate administration of fluids or vasopressors to alter blood pressure. In the first 48 hours following spinal cord injury, the level of neurologic impairment often ascends by 1 to 2 vertebral levels.

Cardiovascular

Spinal cord lesions above the T6 level interrupt sympathetic outflow, resulting in vasodilation, bradycardia, and hypothermia. Even in young, healthy persons, loss of sympathetic tone usually produces supine blood pressure in the range of 100/60 mm Hg. Hypovolemia, infection, or placement in the upright position may precipitate profound hypotension.

In addition to treatment of neurogenic shock, some institutions utilize a protocol management of acute cervical spine and spinal cord injuries based on guidelines developed by the American Association of Neurological Surgeons and the Congress of Neurological Surgeons. These organizations recommend maintenance of mean arterial blood pressure at 85 to 90 mm Hg for the first 7 days following acute spinal cord injury to improve spinal cord perfusion.

Bradycardia that often accompanies hypotension due to cord injury does not require treatment unless symptomatic. Accommodation of the sympathetic and parasympathetic responses usually produces a normal heart rate within 3 to 5 days following injury. However, unopposed vagal stimulation from pain, hollow viscus distension, hypoxemia, or endotracheal suctioning may trigger profound bradycardia. If symptomatic bradycardia not caused by hypoxemia occurs, atropine, isoproterenol, or temporary pacing is useful. It is the loss of compensatory tachycardia early in the course of spinal cord injury that makes iatrogenic pulmonary edema common following even modest fluid administration. If pronounced tachycardia develops in a hypotensive patient with spinal cord injury, another condition such as severe sepsis, internal hemorrhage, or hypovolemia is likely. Because autonomic paresis eliminates crucial vasoconstrictive reflexes, these patients have very limited stress reserves.

Respiratory

Respiratory impairment, the most common complication of spinal cord injury, results from respiratory muscle denervation, rib fractures, hemopneumothorax, lung contusion, and aspiration. Cervical roots 3, 4, and 5 innervate the diaphragm. Therefore, interruption of the cord above this level in an unsupported patient rapidly leads to apnea and death. Cervical spine injuries also cause problems when expiratory muscle weakness impairs cough and secretion clearance. The forced vital capacity (FVC) should be monitored several times daily in the acute phase of spinal cord injury, as further deterioration occurs commonly during this period. As a rule of thumb, such problems are unusual if FVC exceeds 20 mL/kg. If the FVC is less than this value in patients with injuries near the C5 level, compromise of phrenic nerve function should be suspected.

Because quadriplegic patients have little ventilatory reserve, any condition that further impairs work of breathing or mandates increased minute ventilation may lead rapidly to fatigue and ventilatory failure. Lesions above T10 most commonly cause respiratory difficulty by impairing cough, altering
ventilation/perfusion distribution (causing hypoxemia), or decreasing inspiratory capacity. Low lung volumes and atelectasis occur not only because of intrinsic muscle weakness, but also because abdominal distension (often from ileus) limits inspiration. Ventilation may be further compromised by unopposed parasympathetic responses that cause bronchorrhea and bronchoconstriction and increase the risk of vomiting and aspiration. Patients with spinal cord injury are particularly sensitive to the effects of neuromuscular paralytic agents. Although seemingly paradoxical, quadriplegic patients often ventilate best in the supine position. Their only effective muscle of respiration (the diaphragm) is “cocked” into optimal position by such a posture through the upward pressure of the abdominal contents. Conversely, patients with isolated diaphragmatic paralysis ventilate best when fully erect; upright positioning minimizes the cephalad pressure of the abdominal contents against the flaccid diaphragm. This action increases lung volume and helps to stabilize the diaphragm during contraction of the accessory muscles of inspiration. Limitations of vital capacity and forcefulness of cough predispose spinal cord-injured patients to pneumonia.

**Genitourinary**

Urinary tract complications (urinary tract infection, renal failure) are a common cause for late death in spinal cord-injured patients. Continuous urinary catheterization is probably indicated early in the hospital course to monitor urine output. Later, intermittent catheterization is preferred because of its reduced risk of infection. Micturition may be impaired indefinitely following spinal cord injury. Regular surveillance cultures of urine help to detect infection at an early stage. Prophylactic antibiotics may prevent bacteremia but are unlikely to maintain sterile urine in patients with indwelling catheters.

**Gastrointestinal**

Immediately following spinal cord injury, ileus may occur that typically lasts 3 to 4 days. Ileus is likely to be protracted if spinal cord injury is accompanied by retroperitoneal hemorrhage. In most patients, a nasogastric tube should be utilized until bowel sounds return. In spinal cord-injured patients, the combination of tachycardia, hypotension, and absent bowel sounds should prompt consideration of an acute abdomen. (Pain may be absent or atypical because of sensory neurologic deficits.) Often, there is no certain way to rule out intraabdominal catastrophe, short of laparotomy or paracentesis, though abdominal CT can provide some guidance. Pain referred to the shoulder or scapula is a particularly valuable sign of abdominal inflammation in spinal cord-injured patients. Nutrition may be safely withheld for up to a week before caloric supplementation is begun. When ileus resolves, enteral feedings are preferred when feasible because of improved gut function, reduced cost, and avoidance of catheter-related infections. Peptic ulcer disease occurs commonly following spinal cord injury; enteral feeding, proton pump inhibitors, and histamine blockers are useful preventative measures. As soon as bowel sounds return and enteral feeding begins, a program of bowel care with regular evacuation and stool softeners should be started to prevent constipation and impaction. The level of the spinal cord lesion will dictate whether evacuation is spontaneous, reflex, or manually induced.

**Cutaneous**

Skin breakdown is a costly and potentially lethal complication of spinal cord injury that presents a central focus for nursing care. Padding, frequent repositioning, physical therapy, and the use of rotating or air-cushioned beds are helpful in prevention. (The problem of skin breakdown is discussed in detail in Chapter 18.) Spinal cord-injured patients (particularly quadriplegic patients) should not be placed in the prone position because of the possibility of life-threatening hypoventilation, hypoxemia, and bradycardia.

**Miscellaneous**
After the return of spinal reflexes, patients with lesions above the T6 level may develop episodes characterized by hypertension, diaphoresis, piloerection, and flushing. This syndrome, termed autonomic hyperreflexia, must be recognized because it can prove fatal unless rapidly reversed by a simple expedient decompression of an overdistended viscus (usually bowel or bladder). In patients with excessive sympathetic activity, a vagally mediated compensatory bradycardia often occurs. Thromboembolism is nearly universal in the first 90 days after cord injury if patients are left unprotected. Altered autonomic reflexes accentuate the hemodynamic impact of embolism. Prophylactic anticoagulants are effective, but there are risks of provoking spinal hemorrhage in the early phase. The combination of elastic and pneumatic compression stockings is usually used until anticoagulants can be safely administered.

**BRAIN DEATH**

Because the brain is the organ most sensitive to deprivation of oxygen and perfusion, its function may be irretrievably lost despite preservation of other bodily functions. For example, most cases of hypoxic brain injury do not meet the criteria for brain death. Firm criteria for diagnosing brain death are important to prevent wasting valuable medical resources and conversely to avoid premature abandonment of hope for potentially salvageable patients. The definition of brain death is deceptively simple. Brain death is defined as the irreversible loss of function of the brain including the brainstem. The difficulty sometimes lies in the confirmation of the term irreversible. The duty of the physician is exclusion of any reversible cause that can mimic clinical findings of brain death (unresponsiveness, absent brainstem reflexes, demonstrated apnea on a standardized apnea test). To diagnose brain death, the etiology of coma must be known with reasonable certainty. Ideally, MRI or CT scan of the brain demonstrates an acute CNS catastrophe consistent with brain death. In addition, the temperature of the patient must be above 32°C, and evidence of drug intoxication (illicit or iatrogenic) and poisoning must be sought and ruled out. Finally, no endocrine abnormalities or other metabolic derangements can be present, which might explain the clinical state of the patient. Hypothermia, drug overdose, profound hypercarbia, neuromuscular blockade, and shock must be excluded. It should be reasonably concluded that no significant quantity of sedative, narcotic, or anesthetic drugs remain in the body. Furthermore, if clinical criteria alone are used to determine brain death, the patient is best observed over a period of time (approx. 24 hours) to document the stability of the clinical picture. Seizure activity and decerebrate or decorticate posturing are inconsistent with the diagnosis; however, reflexes of purely spinal cord origin are compatible with brain death.

To confirm brain death, cerebral function must be absent at hemispheric, midbrain, pontine, and medullary levels on serial exams or exams with complimentary imaging. Lack of cortical function is evidenced by a totally unreceptive and unresponsive state. Patients in a persistently vegetative state lack awareness and responsiveness but appear awake because RAS arousal pathways remain intact. Such patients do not meet brain death criteria. Patients with destructive lesions of the base of the pons that give rise to the “locked-in” syndrome also appear unresponsive. Careful testing, however, reveals awareness but inability to respond, except for eye opening and vertical eye movements. Midbrain death is confirmed by demonstrating the absence of pupillary, corneal, oculocephalic, oculovestibular, and gag reflexes. Absent pupillary activity indicates loss of midbrain function. Inability to evoke eye movements confirms lost pontine function. Medullary dysfunction is ensured by demonstrating apnea when the patient is challenged by a hypercapnic stimulus. Apnea testing is performed by interrupting positive pressure ventilation while continuing oxygenation support, usually via flow from a tracheal catheter. After preoxygenation, supplemental O₂ is supplied and the patient is observed for
respiratory effort over a prolonged period of time. Such precautions ensure that the patient remains adequately oxygenated though unventilated. A PaCO$_2$ greater than 60 mm Hg or a rise in PCO$_2$ by 20 mm Hg must be attained to ensure adequate ventilatory stimulation. In apneic patients with intact circulation, the PaCO$_2$ normally rises 3 to 5 mm Hg/min. Therefore, knowledge of the baseline PaCO$_2$ can be used to predict the apneic time necessary to ensure a PaCO$_2$ above 60 mm Hg. (In general, 5 to 10 minutes of apnea are required if the baseline PaCO$_2$ is normal.)

For legal reasons, some localities require confirmatory EEGs, somatosensory evoked potentials, brain perfusion scans, transcranial Doppler flow studies, or other tests to document absence of cerebral activity or perfusion, but rarely are such tests necessary to establish a medical diagnosis of brain death. Two common exceptions are patients with high spinal cord injury who will always "fail" the apnea test because of the inability to power ventilation and patients with severe chronic lung disease who are unresponsive to the breath-stimulating effects of hypercarbia. Confirmatory testing may also be helpful in the morbidly obese patient where respiratory effort can be difficult to detect. Even confirmatory tests are not foolproof. Isoelectric EEGs have been recorded for days after presentation of patients with drug-induced coma and may also occur in patients who have lost cortical function but who retain brainstem activity (neocortical death). Such patients usually demonstrate a vegetative state in which arousal is intact but awareness is lacking. Brain death may also be confirmed by using contrast angiography or a nuclear medicine perfusion scan to demonstrate absence of cerebral blood flow.

SUGGESTED READINGS


Chapter 35
Chest and Abdominal Trauma

• Key Points
1. Early consultation with a surgeon is essential whenever a patient with possible intrathoracic or intra-abdominal injury is brought to the emergency department. After stabilization of the vital functions, evaluation and management vary depending on mechanism of injury.
2. Victims of chest trauma who survive to hospital admission have a relatively good prognosis and generally do not require thoracotomy; rib and sternal fractures and pulmonary contusions are the most common injuries.
3. Ensuring that the airway is patent and respiratory drive is adequate is the critical first step. Securing adequate venous access and draining pneumothoraces or hemothoraces are the next priorities.
4. In the setting of thoracic trauma, hypotension is assumed due to hemorrhage unless proven otherwise. If the neck veins are flat, hemorrhage is most likely; if the neck veins are distended, cardiac tamponade and tension pneumothorax are leading candidates. Classic symptoms, however, are frequently absent. Myocardial dysfunction secondary to blunt cardiac injury, infarction, or stress cardiomyopathy should be considered.
5. Tracheobronchial injury should be suspected when hemoptysis or a large bronchopleural fistula is present. Early evaluation by bronchoscopy is indicated, and the injured lung may be excluded by selective one-lung ventilation.
6. Hemothorax, widening of the mediastinum, an arm/leg pulse or blood pressure deficit, thoracic inlet hematoma, and multiple rib or sternal fractures serve as clues to major vascular injury. Patients with these signs should be evaluated by CT angiography in a setting where endovascular therapy and thoracotomy are immediately available.
7. The hemodynamically abnormal patient with evidence of blunt abdominal injury should be rapidly assessed by ultrasound and selected radiographs for intra-abdominal bleeding or contamination from the gastrointestinal tract. CT scanning may be used in hemodynamically normal patients in whom the abdomen cannot be evaluated or pain and tenderness persist.
8. All patients with penetrating wounds in proximity to the abdomen and associated hypotension, peritonitis, or evisceration require emergent laparotomy. Patients with gunshot wounds that traverse the peritoneal cavity or vascular retroperitoneum on physical examination or routine X-rays also require laparotomy.
9. Abdominal compartment syndrome, an often subtle consequence of both surgical and external trauma and resuscitation, can impair pulmonary and renal function. Visceral hypoperfusion precipitates metabolic acidosis and proceeds to vascular collapse unless the abdomen is rapidly decompressed by laparotomy.

INITIAL APPROACH TO THE INJURED PATIENT
Patients are evaluated and their treatment priorities defined according to identified injuries, vital signs, and injury mechanism. In severely injured patients, sequential treatment priorities are established based on overall patient assessment. Vital functions must be evaluated quickly. The management sequence consists of a rapid initial primary survey with coincident resuscitation of vital functions, followed quickly by a more detailed secondary survey, and finally initiation of definitive care. This process constitutes the ABCDEs of trauma care and identifies
life-threatening conditions by considering:

- Airway protection with cervical spine evaluation
- Breathing and ventilation
- Circulation with hemorrhage control
- Disability or neurologic status
- Exposure of the patient with avoidance of hypothermia

Rapid initial assessment of an injured patient can be conducted by identifying oneself and asking the patient for his or her name and what happened. An appropriate response suggests that there is no major airway compromise, breathing is not severely affected, and there is no major decrease in level of consciousness. Failure to respond to these questions suggests significant abnormalities in airway maintenance, breathing, or circulation that require immediate assessment and further management.

The secondary survey begins when evaluation of the ABCDEs is complete and resuscitation is under way. The secondary survey is a head to toe evaluation featuring a complete history and physical examination including reassessment of all vital signs and each region of the body. During the secondary survey, a complete neurologic examination may be performed that should include a repeat Glasgow Coma Scale. Imaging and laboratory studies are also performed at this time. Because patient responses rapidly evolve, repeated physical examinations are required.

**CHEST TRAUMA: EPIDEMIOLOGY**

Almost 500,000 Americans suffer chest trauma each year, accounting for approximately 20% of all hospital-treated injuries. Chest injuries directly result in 20% to 25% of all trauma deaths and may contribute significantly to mortality in another quarter of them. The chest wall, pleural space, and lungs are involved in the great majority of chest injuries (Table 35-1). Although serious burns, crush injuries, and gunshot wounds account for considerable morbidity, in most cases, wounds are nonpenetrating and result from a misadventure involving a motor vehicle. When a vehicular accident proves fatal, more than one half of the deaths are directly attributable to severe thoracic trauma. Most deaths occur at the scene of the accident as a result of a catastrophic, unsalvageable injury, such as aortic transection or massive neurological injury. Fortunately, most patients survive who live long enough to be transported to a hospital. Until the past quarter century, this was not the case; dramatically improved survival of seriously injured patients has accompanied their care in specialized intensive care environments.

<table>
<thead>
<tr>
<th>Injury</th>
<th>Percentage$^a$</th>
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<tr>
<td>Chest wall</td>
<td>45</td>
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<tr>
<td>Pulmonary</td>
<td>26</td>
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<td>Hemothorax</td>
<td>25</td>
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<td>Pneumothorax</td>
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Table 35-1. Thoracic Organ Injury as a Fraction of All Body Trauma
MECHANISMS OF CHEST TRAUMA

Penetrating Chest Injuries
Knife and gunshot wounds account for the majority of penetrating chest injuries. Of these, knife wounds are more likely to be survivable, as their damage is usually confined to a limited area. The injury caused by a gunshot wound depends not only on the path of the bullet but also on the energy delivered per round, the number of impacting rounds, and the characteristics of the projectile (e.g., solid point vs. expanding hollow point or soft nose). Although the path taken by the projectile can be inferred from the entrance and exit wounds, the trajectory may be altered by ricochet off bony structures, and the damaged tract may be much wider than the narrow path of the missile itself because of the widening explosive effect that accompanies passage of the high-speed bullet through tissue. Moreover, depending on the phase of the respiratory cycle during which entry occurred, a bullet may traverse the diaphragm to injure the high abdominal structures even when entrance and exit wounds align above the costal margin. Bullet wounds below the margin of the scapula posteriorly and below the nipple anteriorly must be considered to involve both the chest and abdomen. Computed tomography (CT), a modality that now allows quick acquisition and reconstructed, multiplanar views, has replaced plain films and various contrast studies as the imaging modality of choice for penetrating and blunt thoracic trauma. Endoscopy and vascular studies play a secondary role after screening CT evaluation but frequently are no longer required. CT scanning can be particularly valuable when a projectile is suspected to traverse the mediastinum. Tracks of stab wounds and gunshot wounds can be followed with CT imaging. Though CT imaging has improved our ability to identify injury to the diaphragm, operative examination remains the gold standard for this specific component of the evaluation.

Blunt Chest Injuries
Blunt chest trauma may result from several mechanisms—direct, indirect, compression, contusion, deceleration, or blast. Blast injuries result not only from the inertial impact of the shock wave but also from decompressive implosion that occurs behind the passing shock wave front. Another important mechanism is spalling—the disruption of interfacial tissues that occurs as the passing shock wave front releases energy in transition between tissue and gas. Because of the latter depth charge-like effect, blast injuries exert disproportionate damage to gas-containing organs, such as the lung.
Blunt chest trauma may produce pneumothorax, neurologic dysfunction, respiratory failure, or cardiovascular instability. The principles underlying our general approach to such problems, which are common across a wide spectrum of critical illness, are detailed elsewhere (see Chapters 4, 8, 24, and 34). The current discussion focuses on those mechanical problems unique to blunt (nonpenetrating) chest injury. Rib fractures, increased intracavitary pressures, and shearing forces are the primary mechanisms producing intrathoracic injury in blunt chest trauma. Abdominal events frequently affect pulmonary and cardiovascular function, and in the trauma context, the abdominal compartment syndrome (ACS) deserves special attention.

**Rib and Sternal Fractures**

During blunt chest trauma, older patients who have inflexible ribs may sustain bony fractures that directly injure the lung at its perimeter. By contrast, the increased chest wall flexibility of younger patients tends to allow direct energy transfer to the intrathoracic organs without rib breakage. In young patients, rib disarticulation is more common than rib fractures but results in similar physiological consequences.

Rib fracture, the most common form of thoracic injury, usually occurs in the midchest (ribs 5 to 9) along the posterior axillary line (the point of maximal stress). The uppermost ribs are damaged less frequently because of their intrinsic strength and protection by the shoulder girdle and clavicle. Therefore, fractures of the upper ribs imply a highenergy blow and should raise concern regarding coexisting injury to the major airways or great vessels. On the other hand, the relative suppleness of the lowermost ribs makes them less prone to breakage. For that reason, fracture of the lower ribs (9 to 11) suggests an unusually powerful regional impact and the possibility of concurrent splenic, hepatic, or renal injuries. The number of rib fractures correlates with the magnitude of impact. The history and clinical examination should raise the suspicion of rib fractures, but even when present, fractures may not be confirmed by conventional radiographic views. (Initial plain chest radiographs fail to reveal as many as one half of all rib fractures.) Although oblique filming is the traditional approach for subtle fracture detection, three-dimensional reconstruction of a helical (spiral) CT represents current state-of-the-art imaging for such problems.

Certain features of the radiograph offer helpful clues to etiology. For example, aligned fractures of multiple ribs ("curbstone fractures") usually result from striking a sharp edge. Cough fractures most frequently involve ribs 6 to 9 in the posterior axillary line. Although cough fractures produce significant pain, they generally are not displaced; therefore, they may be difficult to detect.

Displaced rib ends or fragments cause lung laceration or contusion, pneumothorax, and hemothorax. Because the intercostal and internal mammary arteries are perfused under systemic pressure, large hemothoraces can occur when these vessels are disrupted. Pain associated with rib fractures frequently causes splinting, hypoventilation, secretion retention, and atelectasis—complications that are minimized by adequate narcotic analgesia or epidural analgesia. Fractures of multiple ribs at two or more sites may produce a free-floating, unstable section of the chest wall known as a flail segment. Hypoxemia resulting from contusion and hypoventilation is an almost universal consequence. Forceful displacement also may disrupt chondral attachments, producing a flail sternum. Discovery of a flail sternum should raise concern for underlying blunt cardiac injury.

Sternal fracture implies a forceful blow and usually occurs in high-energy motor vehicle accidents when an unrestrained driver strikes the steering wheel or when automobile shoulder harnesses are used without lap restraints. Complaints of pain and tenderness to palpation are signs indicating that CT of the chest should be considered. Contemporary CT imaging identifies mediastinal vascular injury and is a valued screening tool (along with ultrasound) for pericardial fluid collections. Echocardiography is the optimal noninvasive test for delineation of cardiac chamber function and identification of pericardial fluid collections. Occasionally, the
diagnosis can be made by palpating a “step” where two sternal segments are askew. Although sternal fracture may precipitate respiratory failure and delay weaning by causing pain and altering chest wall mechanics, its greatest significance lies in being a potential marker of associated cardiac and bronchial injuries.

Historically, patients with rib or sternal fractures, regardless of severity, have been managed with pain control, pulmonary toilet, judicious fluid management, and mechanical ventilation, as needed. In an effort to improve clinical and functional outcomes, there has been considerable interest in surgical stabilization of rib and sternal fractures, particularly for patients with flail chest, severely displaced fractures, intolerable pain, or inability to separate from mechanical ventilation. Recent studies demonstrate reduced ICU length of stay and number of ventilator days with surgical stabilization of complex rib and sternal fractures. Early data on longer-term outcomes suggest improved quality of life and better long-term pain management in patients with severe rib fractures who receive surgical stabilization.

Increased Intracavitary Pressures

Abrupt elevation of intracavitary pressures may rupture any air-filled or fluid-filled structure that is not braced for the impact. Leak of orogastric secretions after esophageal rupture may result in mediastinitis or empyema. Alveolar rupture may cause pneumothorax, pneumomediastinum, or pulmonary contusion/hemorrhage. Sudden increases of intra-abdominal pressure (IAP) can rupture the diaphragm, herniating the abdominal contents into the chest. Unprotected by the liver, the left hemidiaphragm is at greater risk. By a similar mechanism, a distended stomach or urinary bladder also may rupture when the chest or abdomen is struck forcefully.

Shearing Forces

To varying degrees, all intrathoracic structures are tethered to adjacent tissues. Consequently, shearing forces produced by differential rates and directions of organ motion may cause visceral or vascular tears. Aortic rupture is the most serious injury produced by this mechanism; however, tracheobronchial disruption also may result from deceleration-induced shearing, as (rarely) may atrial avulsion. Direct blows or rapid deceleration may tear pulmonary microvessels, causing pulmonary contusion. If the leak from these vessels is sufficient to form a discrete fluid collection, a pulmonary hematoma may form.

INITIAL MANAGEMENT OF CHEST TRAUMA

Most chest trauma can be managed with some combination of oxygen, analgesics, fluid replacement, and tube thoracostomy. Thoracotomy is necessary in only 10% to 15% of all cases. Initial therapy should consist of ensuring the ABCs: airway, breathing, and circulation. When patency of the airway, adequacy of ventilatory power, or stability of respiratory drive is uncertain, intubation is indicated. Positive-pressure ventilation is initiated for reduced respiratory drive, unduly labored breathing, or hypoxemia or when pain, sedating analgesia, or profoundly deranged chest wall mechanics prevent adequate spontaneous ventilation. After auscultation of the chest to assess airflow adequacy, ultrasound and radiographic imaging should be strongly considered to search for pneumothorax and intrathoracic vascular injuries. The plain chest radiograph is insufficient to rule out major intrathoracic vascular injury, however. CT imaging has replaced the plain chest radiograph and arteriography in this regard. Tension pneumothorax (discussed later) is of particular concern, as the associated intrathoracic pressures not only impede venous return but also compress the contralateral lung. The ACS, a problem that is caused by edema of intra-abdominal viscera or retroperitoneal bleeding, often develops during the resuscitative phase of management (see following). An ultrasonic survey of vital zones, an extended focused abdominal sonography for trauma (FAST)

that includes the upper abdominal and lower thoracic compartments, pelvic region, and heart, can point to the need for urgent intervention. When it can be undertaken expeditiously and safely, CT adds considerably to the
level of diagnostic confidence. If time permits and uncertainty exists, threedimensional reconstruction of data obtained by volumetric CT scanning can be of particular value in planning therapy. Because patients with chest trauma often suffer severe extrathoracic injuries as well, careful examination should be performed of the head, spine, and abdomen looking for associated trauma. Information regarding the spine can be obtained from torso CT scans.

Although other problems (such as arrhythmias, myocardial infarction, tamponade, or tension pneumothorax) must always be considered, hypotension that occurs immediately after thoracic injury usually is the result of hypovolemia. Therefore, the early insertion of two large-bore peripheral intravenous catheters is essential. At the time of catheter insertion, blood should be obtained for determinations of electrolytes, creatinine, hematocrit, coagulation parameters, toxicologic screening, and blood crossmatching. When surface veins can be cannulated, the need for central venous catheterization is minimal; equivalent or greater volumes of fluid can be infused per unit time through large peripheral catheters, and there is real risk of iatrogenic complications from central line placement in the busy setting of the trauma suite. Hypovolemia can result from injury to low-pressure (pulmonary or large systemic veins) or to high-pressure systemic vessels. Bleeding from veins often will subside spontaneously, whereas arterial disruption usually requires open surgical intervention or, in selected cases, endovascular stent repair or embolization. Hypotension is not always the result of hypovolemia; pneumothorax and cardiac tamponade cause hypotension, partly by impeding the return of venous blood to the heart. Hence, constant vigilance must be maintained for the development of neck vein distension or a newly silenced hemithorax hyperresonant to percussion. Note that in the hypovolemic trauma patient, neck vein distention, commonly seen with impaired venous return in other settings, may not be present.

FIGURE 35-1. Patterns of tracheal injury in blunt chest trauma.

SPECIFIC CONDITIONS
The problems of pneumothorax and barotrauma are covered in detail in Chapter 8.

Bronchial and Tracheal Disruptions
Fractures of the first two ribs, sternum and clavicle, are the most common bony injuries associated with airway disruption. Hemoptysis, lobar or whole lung atelectasis, subcutaneous emphysema, pneumomediastinum, and pneumothorax that fail to improve with tube thoracostomy are potential signs of major airway disruption. (The occurrence of bilateral pneumothoraces after blunt trauma strongly suggests this possibility.) Most (>80%)
Airway disruptions due to blunt trauma occur within 2 cm of the carina in the form of spiral tears of the main bronchi or longitudinal tears in the posterior membranous portion of the trachea (Fig. 35-1). Timely recognition and management of airway disruption is important to avert the atelectasis, infection, and bronchial stenosis associated with delayed repair. Fiberoptic bronchoscopy allows detection of major airway injury and facilitates selective intubation with a dual-lumen tube. On the affected side, an attempt is made to position the inflatable cuff distal to the site of disruption. Partial disruption may not be detected until bronchial stenosis and atelectasis occur several weeks later. Because complete disruption generally is recognized and repaired earlier than partial disruption, it is associated with fewer long-term complications. It is also possible to use the bronchoscope to cannulate the functioning lung and, by intubation of one main bronchus, isolate the injured airway and/or lung.

**Hemothorax**

The presence of blood in the pleural space (hemothorax) can arise from either thoracic or abdominal sources. Thoracic sources include lacerated lung parenchyma, torn intercostal or internal mammary arteries, and heart and great vessels. Hemothorax may be generated by an abdominal source in the setting of diaphragmatic laceration with associated abdominal injury—typically to the liver or spleen. On CT images, Hounsfield unit quantitation confirms the presence of blood in the chest. Arteriography is usually definitive and may be therapeutic if embolization of bleeding vessels proves feasible.

Management of hemothorax is based on evacuation of blood from the pleural space to allow lung reexpansion. Typically, this is accomplished with tube thoracostomy. Apposition of visceral and parietal pleura facilitates definitive control of hemorrhage. Patients presenting many hours after injury with a large hemothorax typically have slow accumulation rather than rapid bleeding, particularly if hemodynamically stable. If an acute hemothorax cannot be drained because of clotting in the chest tube, operative drainage may be necessary. Surgical options include open thoracotomy (more likely in the acute setting) or video-assisted thoracoscopic surgery for chronic collections.

In general, observation in a monitored setting is appropriate for patients remaining hemodynamically stable who have limited ongoing hemorrhage from the chest tube. Follow-up chest X-ray should be obtained to confirm evacuation of the pleural space. Repeat chest X-ray during the period of observation may confirm that newly reduced chest tube output is not due to obstructive clotting. The need for emergent thoracotomy is suggested when initial output from the chest tube exceeds 1 L of blood or, when a lower initial volume is drained, output continues to be greater than 200 mL/h for 4 hours.

**Pericardial Tamponade**

Traumatic tamponade may be the result of aortic root disruption, coronary artery laceration, or rupture of the free ventricular wall. When cardiac rupture occurs, it usually arises from the right atrium or ventricle and proves rapidly fatal. Early recognition of pericardial tamponade and prompt decompression and control of hemorrhage are the key contributors to patient survival following cardiac injury. The diagnosis of tamponade should be suspected when muffled heart sounds, hypotension, tachycardia, and elevated jugular venous pressure are noted. Such findings assume heightened significance when a fractured sternum is discovered. (Note that in hypovolemic patients, signs of elevated central venous pressure may be absent.) Rising intrapericardial pressure produces abnormalities in hemodynamic performance and cardiac perfusion, which initially restrict ventricular filling and later diminish cardiac output, causing systemic signs of hypoperfusion. Unrecognized tamponade concludes with cardiovascular collapse and cardiac arrest. The classic picture of injury—muffled heart sounds, hypotension, tachycardia, and jugular venous distension—is frequently incomplete or unclear in the trauma room. Ultrasonography supports the diagnosis by demonstration of pericardial fluid or diastolic collapse of the
right ventricle.

Anesthetic agents should be administered with extreme caution in untreated acute tamponade. Invasive hemodynamic monitoring may be useful but often is not needed. In general, subxiphoid pericardial drainage confirms the diagnosis and is therapeutic. After pericardial drainage and hemodynamics are stabilized, the chest may be fully opened and injuries causing tamponade definitively addressed.

**Cardiac Injury**

Cardiac contusion should be considered whenever a convincing history indicates a significant blow to the chest (e.g., high-speed steering wheel or shoulder harness injury). Sternal fracture without other findings does not predict blunt cardiac injury or warrant monitoring. Common consequences of cardiac contusion include arrhythmias (most common), myocardial ischemia, and conduction system defects (particularly heart block). Ventricular and supraventricular extrasystoles arise very commonly.

Contusion may transiently produce “stunned myocardium,” impairing cardiac output. Elevated troponin levels help to confirm the diagnosis. Although the electrocardiogram (ECG) may demonstrate ST segment elevations that simulate myocardial infarction, reciprocal changes and Q waves are characteristically absent. Echocardiography, the modality of choice for acute evaluation, may reveal a focal area of hypokinetic myocardium. The supportive treatment of cardiac contusion includes close monitoring for arrhythmias, pump failure, and pericardial distention.

Although any cardiac valve may be damaged by a severe blow to the heart, aortic and mitral injuries occur most commonly. Disruption of the tricuspid valve is implicated by a physical examination that demonstrates large jugular V waves and a systolic murmur that varies with respiration. Rupture of the chordae or papillary muscles can result in mitral valve insufficiency. Classically, evidence of reduced forward cardiac output is combined with a murmur, thrill, or overt pulmonary edema. Distinguishing among tamponade, valvular disruption, and cardiac rupture can be accomplished using surface echocardiography, transesophageal echocardiography, or diagnostic cardiac catheterization (see Chapter 2).

**Aortic Disruption**

The healthy aorta of a young person can withstand massive uniform elevations in transmural pressure but tolerates the shearing forces of impact injuries much less well. Most aortic ruptures occur just distal to the ligamentum arteriosum. (In a minority of cases, disruption occurs at the aortic root just above the aortic valve, in which case tamponade is commonly produced.) When rupture of the ascending aorta occurs, damage to the aortic valve or coronary arteries also is possible. Clues suggesting a high likelihood of such vascular injuries include a fatality in the same vehicle, fracture of the steering wheel, lateral impact at high speed, being an “ejected” passenger, or a fall from a height greater than 30 ft.

Aortic transection, a result of abrupt deceleration, usually is fatal at the accident scene. Patients surviving to reach hospital have far better outcome. Remarkably, obvious evidence of external trauma is not detectable in many patients with aortic transection; neither rib nor sternal fractures are required for diagnosis. Typically, chest pain penetrates to the interscapular region. Aortic transection may present as a stroke syndrome if the carotid or vertebral circulation is compromised. Occasionally, disruption of the aorta produces acute paraplegia as the anterior spinal artery takeoff is damaged. Some radiographic clues to aortic transection are illustrated in Figure 35-2. Thoracic CT angiography has replaced contrast angiography as the diagnostic modality of choice (Fig. 35-3). Tears and disruptions of the pulmonary artery rarely occur in the absence of penetrating injury. Many aortic injuries are now repaired nonsurgically using endovascular stents (Fig. 35-4).

**Diaphragm Injuries**
Blunt trauma may rupture the diaphragm, herniating the abdominal contents into the chest. Nearly all such ruptures are left-sided because the liver shields the right hemidiaphragm from direct injury. Disruption of the right hemidiaphragm suggests massive injury force. Major clues to diaphragmatic injury include a left-sided infiltrate or atelectasis, combined with signs and symptoms of bowel obstruction. Hearing bowel sounds above the expected diaphragmatic level on physical examination and seeing an irregular dome conformation with air-fluid levels above the margins of the diaphragm on the chest radiograph also are suggestive. CT scanning or plain radiographs taken after placement of contrast in the bowel may be confirmatory (Fig. 35-5). In subtle cases, injury may only be ruled out at laparoscopy or laparotomy.

FIGURE 35-2. Radiographic clues to aortic disruption include the following: (1) mediastinal widening (best detected on upright films), (2) apical pleural capping, (3) fractures of the first two ribs or sternum, (4) depression of the left main bronchus, (5) indistinct aortic knob, and (6) pleural effusion (shown here for a supine exposure with “ground-glass” appearance of left lung field).
Flail Chest

Flail chest results from multiple contiguous fractures of bony ribs or cartilaginous attachments that dislodge a free-floating section of rib cage or sternum. Restrained by negative intrapleural forces, the floating segment lags during inspiration, producing an apparent “paradoxical motion” during forceful breathing. This instability may go unnoticed until vigorous efforts cause major swings in intrapleural pressure. Flail chest should be suspected in every patient with blunt chest trauma, particularly if multiple rib fractures are evident. Whenever possible, a brief period of spontaneous breathing (five to ten breaths) should be observed to bring any flail segment to clinical attention.

A flail segment impairs normal coordinated action of the respiratory muscles and produces regional hypoventilation because of splinting and pain. Hypoxemia is the major consequence of flail-associated lung contusion and secretion retention. Although the work of breathing may be only modestly affected at low levels of ventilation, it rises dramatically during hyperpnea, as breathing efficiency worsens. Because the sternum retains a relatively fixed position and is not located in a strategic position in relation to the
ventilatory function of the rib cage or diaphragm, flail sternum usually is better tolerated than flail segments elsewhere.

FIGURE 35-4. Aortic transection repaired with endovascular stent graft.

A CT scan also demonstrating left blunt diaphragmatic injury provides additional anatomic detail.

FIGURE 35-5. Chest X-ray demonstrating blunt left diaphragmatic injury with herniating gastrointestinal tract. A CT scan also demonstrating left blunt diaphragmatic injury provides additional anatomic detail.

For patients with extensive injury and ventilatory compromise, mechanical ventilatory assistance may help to reduce fluctuations of intrapleural pressure for the 7 to 14 days needed to stabilize the chest wall. It is important to minimize the minute ventilation requirement and to ensure excellent bronchial hygiene with the intent to reduce the respiratory workload before weaning is attempted. Taping, sandbagging, or other attempts at external chest wall stabilization do not significantly lessen pain or improve ventilatory mechanics and may encourage atelectasis. Intercostal nerve blocks may reduce pain without impairing consciousness or ventilatory drive and thereby facilitate the weaning process. Thoracic epidural catheters are the current modality of choice to complement pharmacologic pain relief.
Pulmonary Contusions

A forceful blow to the chest may contuse the lung at the site of impact or cause a “contrecoup” injury. A lung contusion is nothing more than localized tissue bleeding and edema that impair ventilation-perfusion matching, producing hypoxemia that is often severe. Blood-tinged airway secretions and/or hemoptysis may be present. Pulmonary contusion should be considered in all patients with ill-defined chest infiltrates and hypoxemia that develop shortly after chest trauma, particularly when the radiographic abnormality is aligned with the known path of a forceful blow. Within 6 hours of trauma (usually sooner), pulmonary contusions are radiographically visible as localized, nonsegmental infiltrates. Resolution begins within 24 to 48 hours of injury and usually is complete within 3 to 10 days. Pulmonary contusions tend to be less severe in obese patients because of decreased energy transfer to the lung afforded by the thickened chest wall.

Occasionally, pulmonary contusions coalesce to form a pulmonary hematoma that typically appears as a spherical 1- to 6-cm density. A pulmonary hematoma is a large pocket of blood located deep within the pulmonary parenchyma. Hematomas arise from significant vascular disruption and may require weeks to clear. Resolution is often incomplete, leaving a permanent scar. Acute respiratory distress syndrome (ARDS) frequently follows a brief delay. The incidence of ARDS parallels the extent of contusion, with those larger than 20% associated with a dramatically higher incidence. Because propagation of bloody edema through the airways may play an important role in extending the infiltrate, using modest positive end-expiratory pressure (PEEP) and maintaining an upright thorax with slightly dependent lateral positioning of the contused side from the outset of care may be advisable prophylactic measures.

ARDS and Ventilator-Associated Pneumonia

Most principles of lung-protective management of ARDS that pertain during medical illness apply equally well in the setting of acute chest trauma (see Chapter 24). Although open incisions, coexisting soft tissue trauma, long bone or pelvic fractures, concomitant head injury, and the need to protect the spine may complicate proning, the majority of trauma patients with refractory hypoxemia are appropriate candidates for such repositioning. Prevention of ventilator-associated pneumonia is a high priority, as surgical patients are among those most predisposed, and attributable mortality from this complication is significant. Therefore, duration of intubation should be reduced whenever safely possible to do so, and such basic measures as avoidance of nasogastric and nasotracheal tubes, hand washing, semirecumbent positioning, and adequate nutritional support are especially prudent.

Esophageal Rupture (Boerhaave Syndrome)

Esophageal rupture should be suspected in patients with a history of major chest trauma and a pleural effusion, especially if it is left-sided or accompanied by pneumothorax. Empyema following blunt chest trauma should suggest the possibility of esophageal or diaphragmatic rupture with subsequent bacterial contamination of the pleural space. Interscapular, substernal, or epigastric pains are common symptoms, but fever, hypotension, a rapidly accumulating pneumothorax, or a pleural effusion may be the only manifestation. A marked elevation of pleural fluid amylase is often present, a result of leakage of salivary amylase into the pleural space. The diagnosis may be confirmed by observing macroscopic or microscopic food particles in fluid aspirated from the pleural space.

Esophageal rupture is a potentially lethal condition, as diagnosis is frequently delayed. Mediastinitis is the most frequent cause of death. Chest radiographs demonstrate mediastinal widening and gas in the mediastinum or pleural space. Extravasation of swallowed contrast material into the mediastinum or pleural space confirms the diagnosis. Surprisingly, endoscopy is frequently unrevealing, and CT scan may only suggest the problem by demonstrating fluid (with or without gas) in the pleural space and mediastinum. Immediate surgical repair and
Fat Embolism

The fat embolism syndrome may occur within hours to days after trauma. Although fat embolism usually is associated with multiple long bone or pelvic fractures, diabetes, fatty liver, pancreatitis, joint surgery, and sickle cell anemia are other reported causes. It is theorized that lung injury is produced when lipases hydrolyze neutral triglycerides to liberate unsaturated fatty acids toxic to the pulmonary parenchyma. Fat confined to the pulmonary circulation may precipitate diffuse coagulopathy and disseminated intravascular coagulation (DIC). Fat microglobules may even pass through the pulmonary capillary bed to enter the systemic circuit and produce characteristic (if seldom detected) retinal, central nervous system, and skin lesions.

A classic but often incomplete triad of confusion, pulmonary dysfunction, and cutaneous abnormalities characterize this disorder. Symptoms may include cough, dyspnea, and pleuritic chest pain. These complaints often are accompanied by physical findings of fever, rales, tachypnea, and disorientation. Although a petechial rash over the upper torso may be present in the full-blown syndrome, it is unusual in less obvious cases. Serum and urine lipase levels may be elevated, and fat globules sometimes can be found in the urine, sputum, or bronchial lavage fluid. Retinal fat emboli also may be seen. Initially, the chest radiograph is normal in a large percentage of patients, despite severely impaired gas exchange. Decreased lung compliance, impaired diffusing capacity, hypoxemia, and respiratory alkalosis are common respiratory manifestations. In cases of fat embolism-induced ARDS, infiltrates may require 1 to 4 weeks to resolve. Early use of corticosteroids may be helpful, but this practice remains controversial.

ABDOMINAL TRAUMA: EPIDEMIOLOGY

Evaluation and management of the abdomen and pelvis is a challenging component of initial care of injured patients. Penetration occurring anywhere between the nipples and perineum may cause intraperitoneal injury. Mechanism and location of injury as well as hemodynamic status determine management priorities. Unrecognized abdominal and pelvic injury continues to be a major cause of preventable death after truncal trauma.

The abdomen is partially enclosed by the lower thorax. The anterior abdomen includes the area between the costal margins, the inguinal ligaments, and symphysis pubis, with the defining lateral margins at the anterior axillary lines. The majority of the hollow viscera may be involved when there is injury to the anterior abdomen. Because the diaphragm can rise to the fourth intercostal space during full inspiration, fractures of the lower ribs or penetrating wounds below the nipple line can injure abdominal contents. The pelvic cavity, containing the rectum, bladder, and iliac and pelvic vessels, as well as the female reproductive organs, occupies the lower portion of the retroperitoneal and intraperitoneal space.

Blunt Trauma to the Abdomen

A direct blow can cause compression and crushing injuries to the abdominal contents and pelvis. These forces deform solid and hollow organs and can cause rupture with secondary bleeding, contamination by intestinal contents, and associated peritonitis. Shearing injury often results during an automobile crash when a restraining device is worn improperly, causing tangential impact with the abdominal wall. Deceleration injury causes differential movement of fixed and nonfixed parts of the body. Examples include lacerations of the liver, spleen, and small bowel mesentery at the sites of their fixed supporting ligaments. Although the organs most frequently injured from blunt trauma to the abdomen are the spleen, liver, and small intestine, retroperitoneal hematoma and urinary tract damage may occur in patients sustaining vascular or pelvic bony injuries.
Penetrating Trauma to the Abdomen

Stab wounds or low-velocity gunshot wounds cause tissue disruption by laceration and cutting. High-velocity gunshot wounds transfer more kinetic energy to abdominal contents and damage to structures surrounding the track of the missile. Stab wounds most commonly involve the liver, small bowel, diaphragm, and colon. Gunshot wounds may cause intra-abdominal injuries based upon trajectory, cavitation effect, and bullet fragmentation. Gunshot wounds most commonly involve the small intestine, colon, liver, and abdominal vascular structures. Injuries due to a shotgun blast are affected by the type of shot used and the distance from the gun to the patient. Explosive devices cause injury by multiple mechanisms that include wounds caused by penetrating fragments and blunt injuries from the patient being thrown by the blast or struck by debris.

Physical Examination

The patient must be fully undressed to allow thorough inspection. Anterior and posterior abdomen as well as the lower chest and perineum should be inspected for abrasions, contusions, lacerations, penetrating wounds, impaled foreign bodies, evisceration of omentum or bowel, and the pregnant state. The patient should be cautiously log rolled to facilitate examination of the back and flanks. The flank, scrotum, and perianal area should be inspected quickly for blood at the urethral meatus or swelling or bruising or laceration of the perineum, vagina, rectum, or buttocks. Rectal or vaginal lacerations may indicate an open pelvic fracture. Auscultation of the abdomen is frequently difficult in the noisy emergency department. Percussion of the abdomen causes movement of the peritoneum and may elicit signs of peritoneal irritation. If peritoneal irritation is so easily elicited, no additional evidence of rebound tenderness is necessary.

Adjuncts to Physical Examination

Gastric and urinary catheters are frequently inserted as part of the resuscitation phase after initial problems with airway, breathing, and circulation are addressed. Inserting an enteral tube early in resuscitation will relieve acute gastric dilatation, decompress the stomach, and remove gastric contents, reducing the incidence of later aspiration; however, in an awake patient with an active gag reflex, insertion itself may promote vomiting. The presence of blood in gastric contents suggests an injury to the esophagus or upper gastrointestinal tract if nasal and oral sources are excluded. Use of a nasogastric tube should be avoided in patients with facial fractures or fractures of the skull base. In this case, the gastric tube, if used, must be inserted through the mouth. Urinary catheters relieve bladder distention and allow for monitoring of urine output as an index of tissue perfusion. Gross hematuria is a sign of trauma to the genitourinary tract and nonrenal intraabdominal organs. The absence of hematuria does not rule out injury to the genitourinary tract. Inability to void, unstable pelvic fracture, blood at the urethral meatus, scrotal hematoma, and an abnormal prostate on rectal examination are indications for a retrograde urethrogram to confirm an intact urethra prior to insertion of a urinary catheter. If the urethra is torn, insertion of a suprapubic tube may be necessary.

An AP chest X-ray is recommended in the assessment of patients with blunt trauma. Hemodynamically unstable patients with penetrating abdominal wounds do not require screening X-rays in the emergency department. These patients should be expeditiously transferred to the operating room. If the patient is hemodynamically normal and has penetrating trauma above the umbilicus or a suspected thoracoabdominal injury, an upright chest X-ray is helpful to exclude an associated hemothorax or pneumothorax or to document the presence of intraperitoneal air. Marker rings or clips may be applied to entrance and exit wound sites, and a supine abdominal X-ray may be obtained in hemodynamically normal patients to
determine the track of a missile and detect the presence of retroperitoneal air. An AP pelvic X-ray may be helpful in establishing the source of blood loss in hemodynamically abnormal patients and in patients with pelvic pain or tenderness.

Ultrasound may be used to detect the presence of hemoperitoneum (Fig. 35-6). This technology is rapid, noninvasive, accurate, and inexpensive and may be repeated frequently. Another important benefit is the ready availability of such imaging at the bedside. Thus, ultrasound can be performed while simultaneously the clinician is engaged in other diagnostic or therapeutic procedures. Ultrasound may also detect one important nonhypovolemic reason for hypotension: pericardial tamponade. Ultrasound can examine the space about the liver, spleen, and pelvis for evidence of fluid accumulation.

CT requires transport to the scanner, administration of contrast, and scanning of the upper and lower abdomen, as well as the lower chest and pelvis. This procedure should be used in hemodynamically compensated patients in whom there is no immediate indication for laparotomy. The CT scan provides information related to specific organ injury and can diagnose retroperitoneal and pelvic organ injuries that are difficult to assess with similar precision by physical examination or ultrasound. Relative contraindications to CT include delay until the scanner is available, noncooperative patient who cannot be safely sedated, and allergy to contrast. CT inconsistently detects gastrointestinal, diaphragmatic, and pancreatic injuries. In the absence of hepatic or splenic injuries, the presence of free fluid in the peritoneal cavity suggests an injury to the gastrointestinal tract. Intraperitoneal or extraperitoneal bladder rupture is best diagnosed with a CT cystogram. Other suspected urinary system injuries are best evaluated by contrast-enhanced CT. If CT is not available, intravenous pyelography is an alternative.

Patterns of Injury

Duodenal rupture is frequently encountered in unrestrained drivers involved in frontal impact motor vehicle collisions and in patients who sustain direct blows to the abdomen, such as from bicycle handlebars. A bloody gastric aspirate or retroperitoneal air on imaging studies is identified. Injury to the adjacent pancreas also results from a direct epigastric blow compressing the pancreas against the vertebral column. An early normal serum amylase level does not exclude major pancreatic trauma. Persistently elevated or rising serum amylase levels should prompt further evaluation of the pancreas and other abdominal structures. CT imaging may not identify significant pancreatic trauma in the initial period after injury (8 hours); CT should be repeated at a later time if a pancreatic injury is suspected on clinical grounds.

Intestinal injury by blunt and penetrating mechanisms presents differently. Blunt injury to the intestines typically results from sudden deceleration with subsequent tearing near a fixed point of attachment, typically if a seat belt was applied incorrectly (Fig. 35-7). The appearance of transverse linear ecchymoses on the abdominal wall or the presence of a lumbar fracture on X-ray should alert the clinician to the possibility of intestinal injury. While some patients may have early abdominal pain and tenderness, diagnosis may be difficult in others, in part because an injured intestine may only produce minimal hemorrhage. Peritonitis in patients with blunt injury may not develop until hours after the insult. Penetrating injury to the intestines is frequently associated with peritonitis that requires operative intervention. Free air below the diaphragm will frequently be identified on an upright chest X-ray. Patients with obvious peritoneal signs should be transported to the operating room without additional time spent in diagnostic testing.

Solid organ injury involves the liver, spleen, and kidneys. In the presence of shock or hemodynamic instability, urgent laparotomy should be considered. Solid organ injury in hemodynamically normal patients can often be managed without surgery. Embolization procedures can be utilized to control the bleeding of localized injuries identified by CT imaging (Fig. 35-8). Patients with solid organ injury should be admitted for serial physical examination and close observation. Remarkably, simultaneous injury to the intestine occurs in less than 5% of patients initially thought to have injury confined to solid organs.
Direct blows to the back or flank that result in contusions, hematomas, or other soft tissue changes are markers of potential underlying renal or ureteral injury and warrant CT of the urinary tract. Other indications for evaluation of the urinary tract include gross hematuria or microscopic hematuria in patients with penetrating abdominal trauma. The majority of renal injuries are identified by CT and may be managed nonoperatively. Gross or microscopic hematuria in patients with an episode of shock suggests coexisting nonrenal abdominal injuries.
Pelvic Fractures

Patients with hypotension and pelvic fractures have a high associated risk of mortality. Pelvic fractures associated with bleeding commonly include disruption of posterior pelvic ligaments or sacral and iliac fractures and/or dislocations. Disruption of the pelvic ring tears the pelvic venous plexus and occasionally disrupts the internal iliac arterial system. Vertical displacement of the sacroiliac joint may also cause disruption of the iliac vasculature, causing uncontrolled hemorrhage. Injury to the pelvic ring may be caused by high-energy blunt impact, crush injury, and falls from heights. Mortality rate increases progressively in the presence of open fractures or hypotension upon presentation.

Four patterns of force leading to pelvic fracture include AP compression, lateral compression, vertical shear, and combinations of these. With disruption of the symphysis pubis, there is often tearing of posterior ligaments as well as sacroiliac fracture. With opening of the pelvic ring, there can be hemorrhage from iliac vessels or the posterior venous plexus of the pelvis.

Initial management of a major pelvic disruption associated with hemorrhage requires bleeding control and fluid resuscitation. Hemorrhage control is achieved through mechanical stabilization of the pelvic ring and external counterpressure. Initial care frequently involves simple techniques to stabilize the pelvis. A sheet, pelvic binder, or other device can be applied to give stability to the injured pelvis at the level of the greater trochanters of the femur. This external pelvic compression will restrict pelvic expansion and help to tamponade bleeding.

Compartment Syndromes

Over recent years, there has been increased awareness of the presence and importance of torso “compartment syndromes,” particularly of the abdomen. Compartment syndromes, defined as dysfunction or injury of tissues within a closed anatomic space because of a nonphysiologic rise in local pressure, are often subtle but devastating problems encountered frequently in patients who sustain injuries. Closed anatomic spaces at risk include those of the extremities—classically of the lower leg, but also of the arm, hand, and gluteal regions. High tension within these structures is usually suspected during physical examination, and the diagnosis is strongly supported by eliciting pain on passive flexion and by loss of sensation and/or distal pulses of the affected limb. Clearly, the ease of making the diagnosis is compromised in patients who cannot communicate effectively because of sedation, coma, and/or intubation. Confirmation by direct tissue pressure measurement adds to the diagnostic certainty, but the decision for operative release remains a clinical judgment. Wherever encountered, acute compartment syndrome merits rapid surgical intervention, as delayed decompression extends the ischemic period and threatens tissue viability. Localized compartment syndrome may not give rise to the telltale lactic acidosis and muscle enzyme elevations that characterize ischemia of larger muscle compartments (rhabdomyolysis).

Resuscitation from trauma frequently involves the rapid delivery of large volumes of intravenous fluid. If the contents of a potential compartment have been injured and/or the microvessels are unusually permeable, extravasation raises tension within that confined space to levels that may compromise perfusion of the nerves, muscles, and other tissues. Ischemia occurs as the tissue pressures (normally 0 to 10 mm Hg) approach or exceed capillary pressure. Compartment syndrome can develop for reasons other than direct trauma, including local extravasation of intravenous fluids at the site of infusion and spontaneous or iatrogenic arterial hemorrhage. The rise of compartment pressure is not a linear function of extravascular volume leakage. Pressure within a compartment tends to rise slowly until its limits of accommodation are reached, escalating rapidly thereafter.
Table 35-2. Medical Predispositions to Intra-abdominal Hypertension

Massive fluid resuscitation (>5 L in 24 hours)

Ileus (paralytic, mechanical, pseudo-obstructive)

Intra-abdominal infection

Pneumoperitoneum (can include pneumoperitoneum for laparotomy)

Hemoperitoneum

Acidosis (arterial pH ≤ 7.2)

Hypothermia (core temperature ≤33°C)

Polytransfusion (transfusion ≥10 units of PRBCs in 24 hours)

Coagulopathy (platelets ≤55,000/mm$^3$; PTT > 2 × normal; INR > 1.5)

Sepsis (American-European Consensus Conference definition)

Bacteremia (positive blood cultures)

Liver dysfunction (cirrhosis with ascites, portal vein thrombosis, ischemic hepatitis)

Need for mechanical ventilation

Use of PEEP or the presence of auto-PEEP

Pneumonia

PRBCs, packed red blood cells.


Abdominal Compartment Syndrome

Although compartment syndrome was first described in the setting of limb trauma, widespread recent attention has focused on the compartment syndrome developing within the abdomen. The abdominal compartment is bounded inferiorly by the pelvic floor, circumferentially by the abdominal wall, and superiorly by the diaphragm. Elevated intra-abdominal pressure (IAP) occurs in a variety of critically ill patients (Tables 35-2 and 35-3). Intraabdominal tension may raise to dangerous levels in medical (pancreatitis, cirrhosis, peritonitis) as well as in surgical (burns, multiorgan trauma) conditions. Even when no traumatic damage to vessels or organs has occurred, vigorous intravascular volume expansion predisposes to its development.
Table 35-3. Surgical Settings Associated with Intraabdominal Hypertension

Recent abdominal surgery

Open abdomen (may still develop ACS, especially if early postoperative)

Pelvic fractures

Blunt or penetrating abdominal trauma

Abdominal packing after temporary abdominal closure for multiple trauma or liver transplantation

Large-volume fluid resuscitation following trauma

Retroperitoneal bleeding

Although the diaphragm anatomically divides the chest and abdomen, it is not a rigid barrier to transmission of increased pressures within the torso. In fact, increased pressures within the abdomen affect intrathoracic function to a greater extent than changes in intrathoracic pressure impact the performance of abdominal organs. The classic description of ACS included a tense distended abdomen, decreased renal function, elevated peak airway pressure, hypoxemia, and inadequate ventilation. High IAP increases the work of breathing, causes atelectasis, functionally stiffens the chest wall, increases extravascular lung water, and routinely elevates inspiratory airway pressures even when PEEP and tidal volume remain unchanged.

The tissue-compromising effects of raised IAP extend along a broad continuum, with perfusion adequacy or impairment being a function not only of the pressure itself but also of the mean arterial pressure. (Perfusion pressure = mean arterial pressure-intra-abdominal pressure.) The cycle of impaired outflow, decreased capillary perfusion, and increasing pressure decreases hepatosplanchnic and renal blood flows, compresses the inferior vena cava, and impedes venous return to the heart. Declining cardiac output progresses eventually to shock. ACS results in renal dysfunction and oliguria, gut mucosal ischemia, and lactic acidosis that often progresses to life-threatening status. Confusion as to the cause of renal insufficiency often arises when rhabdomyolysis coexists in this posttraumatic setting. Indeed, aggressive fluid infusion aimed at addressing trauma-induced rhabdomyolysis may contribute to the development of ACS. Urinary electrolytes may be of value in sorting out the etiology—prerenal or tubular damage—in the oliguric patient who has not received diuretics.
Diagnosis of intra-abdominal hypertension and ACS is typically established by characteristic physical and laboratory findings and measurement of IAP. The magnitude of IAP is not easily predicted by manual palpation alone; accurate estimation of IAP is most easily accomplished by transduction of bladder pressure (Fig. 35-9) (see Chapter 5 for technique description). The current technique involves instillation of 25 to 50 mL of sterile saline into the bladder via the urinary drainage (Foley) catheter. Catheter tubing is then clamped and bladder pressure is measured via a transducer. Alternatively, IAP is estimated by elevating the drainage tube and measuring the height of the resulting fluid column. No sharp threshold of pressure can be specified that mandates decompressive intervention (massive paracentesis or decompressive laparotomy), as dysfunction may be detectable at vesicular pressures as low as 10 to 15 mm Hg, depending on arterial (and therefore perfusion) pressure. Although intravascular volume administration may help preserve an adequate perfusion gradient when IAP is only moderately elevated, it is generally advised that early decompression be attempted when the IAP exceeds 20 to 25 mm Hg in a clinically compatible setting. It must be emphasized that ACS is defined by the combination of intra-abdominal hypertension and evolving end-organ failure. In the setting of trauma, the ACS appears to be a joint function of the preexisting “tightness” of the abdomen (as reflected imprecisely by the body mass index), the extent and nature of the abdominal injury, and the infused fluid volume. Although technically outside of the normal range and, therefore, both concerning and worthy of tracking, abdominal pressures greater than 15 mm Hg may be recorded in patients without critical illnesses or perfusion compromise.

After trauma, definitive treatment for fully manifested ACS is surgical decompression via laparotomy. Surgical decompression is almost always effective, often immediately and dramatically relieving hypotension, renal insufficiency, and respiratory compromise. It should be noted, however, that an open abdomen does not guarantee low IAP, so that continued surveillance is warranted postlaparotomy. Surgical decompression can be safely performed at the bedside in the intensive care unit. This is an important option to weigh, as many patients with ACS are otherwise unstable from a cardiopulmonary standpoint. Unfortunately, abrupt restoration of blood
flow may sometimes lead to reperfusion injury in visceral organs. Once open, the abdomen often requires many days before reduced tissue swelling allows reclosure to be safely attempted (Fig. 35-10).

**FIGURE 35-10. Temporary abdominal closure in a patient with abdominal compartment syndrome.** Note how the abdominal wall opens because of increased intra-abdominal pressure and the distance between skin edges.

<table>
<thead>
<tr>
<th>Table 35-4. Nonsurgical Treatment Options for Elevated Intraabdominal Pressure</th>
</tr>
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<tbody>
<tr>
<td>Gastric decompression (nasogastric suction)</td>
</tr>
<tr>
<td>Rectal decompression (enemas, rectal drainage catheter/tube)</td>
</tr>
<tr>
<td>Sedation</td>
</tr>
<tr>
<td>Neuromuscular blockade</td>
</tr>
<tr>
<td>Body positioning</td>
</tr>
<tr>
<td>Paracentesis</td>
</tr>
<tr>
<td>Prokinetic agents (stomach: metoclopramide and erythromycin; colon: prostigmine)</td>
</tr>
</tbody>
</table>
Diuretics (alone or in combination with 25% human albumin)

Venovenous hemofiltration/ultrafiltration

When the patient is not acutely compromised, nonsurgical options to relieve abdominal hypertension are available but inconsistently effective. For example, neuromuscular blockade and relief of colonic distention may help, and removal of excess fluid can be attempted by diuretics or ultrafiltration. However, one must insure that fluid removal by these means does not result in impaired oxygen delivery, hypotension, or end-organ hypoperfusion. Percutaneous catheter drainage has also been performed for free fluid or ascites within the peritoneal cavity. Bedside ultrasound may identify a safe anatomic window for placing the drainage catheter. Other methods for decompressing the bowel and stopping peritoneal fluid accumulation in ACS have been reported, with varying efficacy depending on case specifics (Table 35-4).

SUGGESTED READINGS


Chapter 36
Acute Abdomen

• Key Points

1. Patients in the ICU may not have typical presentations of acute abdominal conditions—low-grade fever, mild agitation, or tube feeding intolerance may be the only clues.

2. A pulmonary process, such as pneumonia, may cause ileus or mimic an acute problem below the diaphragm.

3. Ultrasound is an excellent first imaging method for lesions suspected in the pelvis and those adjacent to the liver, spleen, or kidneys. CT scanning is better for imaging the entire abdomen, but drawbacks include lack of portability and the need for radiation exposure.

4. When caring for patients with suspected abdominal disasters, (1) assume that the most life-threatening possibility is causative, (2) avoid obscuring symptoms with excessive sedation or analgesics, (3) reexamine the patient regularly, (4) involve surgical and/or gynecologic consultants early in the evaluation, and (5) carefully select diagnostic tests most likely to give an expeditious and definitive answer.

5. A patient's age, gender, and underlying illnesses provide valuable clues to specific diagnoses, even in the absence of a detailed history.

6. Ethanol and gallstones account for most cases of acute pancreatitis. Of these two entities, gallstone-induced pancreatitis is the more important diagnosis to make because biliary obstruction often requires urgent surgical intervention. Prompt surgical or endoscopic decompression of the biliary tract can abort some episodes of acute pancreatitis.

PRINCIPLES OF MANAGEMENT

The problems of hepatic failure and gastrointestinal (GI) bleeding are discussed separately in Chapters 31 and 37, respectively. Diseases causing acute abdominal pain may not present in a typical fashion in the intensive care unit (ICU) population. Intolerance of tube feeding or loose stools can be the first signal of an evolving abdominal crisis. Moreover, the single most important part of the diagnostic evaluation, the history, is often difficult or impossible to obtain. Patients with spinal cord injuries, those in coma, and those receiving corticosteroids or neuromuscular paralytic drugs may experience an abdominal catastrophe with few signs or symptoms. Therefore, ICU patients should undergo frequent abdominal evaluations, and a low threshold of suspicion for serious problems should be maintained.

Several principles should be kept in mind when critically ill patients with acute abdominal pain are being evaluated: (1) Carefully exclude emergent nonabdominal processes such as myocardial infarction. (2) Until a firm diagnosis is established, consider the problem to be urgent and potentially life threatening. (3) Make repeated observations—a changing examination provides valuable clues to diagnosing abdominal disorders. (4) Involve a surgeon and/or gynecologist early in the evaluation. (All consultants will benefit by following the evolution of the illness; furthermore, this strategy avoids unnecessary repetition of painful pelvic and rectal examinations.) (5) Avoid excessive use of analgesics or sedatives in patients with undiagnosed conditions. (6) Withhold enteral feedings and enteral medications in the setting of intestinal dysfunction or when laparotomy may become necessary.
DIAGNOSIS

History

An accurate history is essential. Description of the onset and character of the pain as well as exacerbating or relieving factors is helpful in diagnosis. Classic patterns of abdominal pain are seen in Figures 36-1 and 36-2. All conscious patients should be asked to localize the pain to a discrete site with one finger.

Sustained abdominal pain awakening the patient from sleep or undiagnosed pain persisting more than 6 hours usually represents a surgical problem. Acute abdominal pain generally arises from one of three mechanisms: (1) visceral ischemia, (2) serosal inflammation, or (3) distention of a hollow viscus. Pain of sudden onset suggests a vascular catastrophe or perforation of a hollow viscus. Pain of gradual onset that builds to a crescendo is more typical of hollow viscus overdistention, as is intermittent pain in a “colicky” pattern. Steady pain suggests serosal inflammation, especially when it is markedly exacerbated by changes in position or local pressure (e.g., rebound tenderness). A pleuritic component raises the possibility that an “intra-abdominal process” either abuts the inferior surface of the diaphragm or actually extends into the chest. (This is why lower lobe pneumonia, empyema, and heart may be mistakenly diagnosed as an acute abdominal problem.)
FIGURE 36-1. Referred pain and shifting pain in the acute abdomen. *Solid circles* indicate the site of maximum pain; *dashed circles* indicate sites of lesser pain. (Adapted from Doherty GM. The acute abdomen. In: Doherty GM, ed. *Current Surgical Diagnosis and Treatment*. 13th ed. New York: McGraw-Hill/Lange; 2009: Figure 21-2, pg 453.)

New symptoms associated with the pain, such as nausea or vomiting, or change in bowel or urinary habits are extremely helpful. For obvious reasons, a history of hematemesis or hematochezia is informative. A detailed gynecologic history is essential in all female patients, with special attention to previous gynecologic problems or changes in menstrual pattern.
Physical Examination

The patient's resting position can be a clue to the cause of abdominal pain: patients with peritonitis often lie motionless because any movement exacerbates pain; those with pancreatitis get relief by sitting up and leaning forward and are often found in this position. Patients with biliary colic or nephrolithiasis often are unable to remain still, writhing in pain. The abdomen should first be examined visually, then auscultated, percussed, and finally palpated. Simple inspection may reveal distention produced by ileus, ascites, or mass (or rarely) the discoloration of Grey-Turner or Cullen signs of pancreatitis. Auscultation may reveal a silent abdomen in established peritonitis, high-pitched bowel sounds of partial obstruction, or perhaps even a friction rub associated with splenic infarct or pneumonia. Percussion can distinguish distention from gas (tympany) and ascites, blood, or tumor (dullness), and in a patient with peritonitis, the reaction to percussion may obviate the need for deep palpation. Palpating the abdomen as the first part of the examination is likely to produce voluntary guarding or induce bowel sounds, even in patients with severe ileus. The most painful area of the abdomen should be examined last. Rectal and pelvic examinations must be performed in appropriate patients. Rectal examination may detect colonic impaction, tumor, GI bleeding, and the localized tenderness of retrocecal appendicitis. Pain associated with hip flexion and radiating to the back suggests a retroperitoneal process. Pelvic examination should search for evidence of pelvic inflammation, fallopian tube infection, and ovarian masses. When completed, the abdominal
questions: (1) Is there rebound tenderness? (2) Are the bowel sounds absent? (3) Are there palpable masses? (4) Is there evidence of free air or fluid in the abdomen? An affirmative answer to any of these questions strongly indicates that surgical evaluation will be necessary. Peritoneal signs are the most reliable in predicting the need for urgent laparotomy. The development of shock in a patient with an acute abdomen is also highly indicative of a need for surgery.

**Routine Laboratory Tests**

Routine laboratory tests are rarely diagnostic. Leukocyte counts and differentials may be normal even with severe intra-abdominal disease. A reduced hemoglobin value may indicate slow chronic blood loss or acute severe hemorrhage with volume replacement. The serum amylase and lipase can be helpful if pancreatitis is suspected, but both false-negative and false-positive results occur. Similarly, elevations in hepatic transaminase, bilirubin, or alkaline phosphatase levels suggest liver, gallbladder, or biliary tract disease but are nonspecific. Although commonly done, separate determinations of conjugated and unconjugated bilirubin are of little value. The combination of acutely elevated bilirubin and alkaline phosphatase is probably most helpful, suggesting obstructive biliary tract disease. A triad of hyperkalemia, hyperphosphatemia, and metabolic (lactic) acidosis (in the absence of renal failure) suggests advanced bowel infarction. In the appropriate clinical context, an isolated elevation of lactate may reflect onset or progression of bowel ischemia. Laboratory findings such as these should motivate additional imaging or serial physical examinations, as discussed below. Bladder pressure measurements should also be considered if abdominal compartment syndrome (ACS) is a possibility. A rapid, sensitive pregnancy test should be obtained in the evaluation of any potentially fertile woman because ectopic pregnancy represents a potentially fatal cause of abdominal and pelvic pain and because an intrauterine pregnancy dictates important diagnostic and management choices.

**Plain Radiographs of the Abdomen**

Although now overshadowed by the more informative computed tomography (CT) scan, the plain abdominal radiograph may quickly provide clues to the etiology and urgency of acute abdominal pain. In patients with acute abdominal pain, supine and upright films of the abdomen may be helpful but are rarely diagnostic. For example, even when the film reveals “free air,” such a finding supports gut perforation but does not localize the site of perforation. (Rarely, free intra-abdominal air may originate from pulmonary barotrauma and gas dissection.) Similarly, finding multiple air fluid levels in small bowel does not precisely identify the site of bowel obstruction. Radiographic signs that should be sought include (1) calcification, (2) mass effect, (3) extraluminal gas, (4) effacement of normal soft tissue planes, (5) localized ileus, (6) thumbprinting of bowel, and (7) evidence of gas in the biliary tree. Because it is difficult, if not impossible, to obtain upright films in the critically ill, lateral decubitus views frequently must be substituted. An upright chest radiograph should also be reviewed in all patients with acute abdominal pain to look for subdiaphragmatic air or a lower lobe pneumonia.

**Ultrasound**

Ultrasound (US) examination utilizes high-frequency sound energy to define anatomic structure and, when combined with Doppler technology, characterizes blood flow. Because wound dressings, adipose tissue, and air-tissue interfaces deflect ultrasonic energy, US is often disappointing in the obese or in patients with prominent bowel distention or abdominal surgical dressings. Quality US also requires specific skills to perform and interpret. Frequently, views generated by ultrasound may be difficult to evaluate by the nonradiologist (unlike CT images). US has the desirable features of being portable, rapidly accomplished,
relatively inexpensive, and devoid of ionizing radiation and contrast media.

For women, US is an excellent method for detecting pelvic processes (e.g., ectopic or intrauterine pregnancy, ovarian cysts, or pelvic tumors) and for staging normal pregnancy. Likewise, because a bowel gas interface does not usually need to be crossed by the beam in the right upper quadrant, US is outstanding for viewing the liver and gallbladder. US is of high value in detecting cholelithiasis, biliary tract dilation, and pericholecystic fluid or edema. Clear images of the kidneys and ureters can also be routinely obtained because they can be imaged from the dorsal aspect, thereby avoiding overlying bowel gas. Fluid may also be identified adjacent to the spleen. When searching for gallstones or pelvic processes in a woman, US is as good as any imaging modality. However, the extent of bowel gas makes visualization of the pancreas inconsistent.

**Computed Tomographic Scanning**

Although it has limitations relative to cost, radiation exposure, and portability, CT is superior to ultrasound for imaging the abdomen. Because the abdominal CT now provides amazing image quality with high sensitivity, it has supplanted most other imaging modalities and, in many situations, is more useful than the physical examination in the ICU population. The CT scan requires transport of the patient to the radiology suite, but in contrast to magnetic resonance scanning, it offers dramatically more rapid imaging and is not precluded by the presence of metallic devices. CT images are easier to interpret than sonograms, especially for the nonradiologist, and they offer high-resolution views of essentially every intra-abdominal and retroperitoneal structure. Enteral contrast material may help distinguish the bowel lumen from other gas or fluid-filled structures such as abscesses. The CT scan requires iodinated contrast material to evaluate vasculature.

**Magnetic Resonance Imaging**

The magnetic resonance imaging (MRI) has significant limitations in the ICU patient population because of the requirement for transport to the scanner, the relatively long scanning times, the need for a motionless patient, and the prohibition of metallic support devices. Brain and soft tissue detail, however, is superb. MRI should also be considered for imaging in the pregnant patient with abdominal pain, as it avoids exposure to ionizing radiation.

<table>
<thead>
<tr>
<th>Table 36-1. Characteristics of CT, MRI, and US Examinations</th>
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<tbody>
<tr>
<td><strong>Computed Tomography</strong></td>
</tr>
<tr>
<td>Not portable</td>
</tr>
<tr>
<td>Expensive</td>
</tr>
<tr>
<td>Can evaluate through wounds and bandages</td>
</tr>
<tr>
<td>Better in overweight patients</td>
</tr>
<tr>
<td>Cross-sectional views best</td>
</tr>
</tbody>
</table>
Metal causes artifact
Impossible with metal implants
Air causes artifact

Static images
Static images
Dynamic images possible

Uniform resolution across field
Uniform resolution across field
Limited area of high resolution

Not operator dependent
Not operator dependent
Highly operator dependent

Requires intravenous contrast to distinguish vessels
Exquisite detail of flowing blood and soft tissues
Cystic and dilated structures provide best contrast; air interferes

Intravenous contrast nephrotoxic
Gadolinium contrast toxic in renal impairment
Nontoxic

Biliary Scans
The performance of biliary tract scans relies on the use of a radioactive analog of hepatobiliary iminodiacetic acid (HIDA) that, after administration, is taken up by the liver and excreted into the bile, where it outlines the major intrahepatic ducts, gallbladder, and common bile duct. Radionuclide scans (“HIDA” scans) are sensitive but lack specificity for biliary tract inflammation, particularly in the absence of gallstones. The high sensitivity of these tests renders them useful for excluding the diagnosis of cholecystitis, provided an adequate study is obtained. Failure to visualize the gallbladder may result from obstructive biliary tract disease, starvation, total parenteral nutrition (TPN) use, or severe parenchymal liver failure—often the very problems necessitating ICU admission. Hepatobiliary scan data, however, can provide complementary function assessment that often adds value to the other anatomic imaging modalities. Various imaging modalities available are outlined in Table 36-1.

SPECIFIC CONDITIONS PRODUCING THE ACUTE ABDOMEN
Although age alone never makes nor excludes a specific diagnosis, a patient's age does give valuable clues to diagnosis (Table 36-2). Similarly, the etiology of abdominal discomfort varies, depending on whether the pain precipitated ICU admission or developed while the patient was in the ICU. Although ruptured ectopic pregnancy, aortic rupture, and pancreatitis rarely develop in ICU occupants, cholecystitis, appendicitis, bowel ischemia, and ulcer perforations sometimes do. The most rapidly lethal condition compatible with the presentation should be considered first, particularly in patients with overt abdominal signs and hypotension. The fulminant development of shock associated with acute abdominal pain is usually attributable to vascular disruption with intra-abdominal hemorrhage or to severe sepsis. Two conditions of this type in most urgent need of surgical intervention are ruptured abdominal aortic aneurysm and ruptured ectopic pregnancy.

Ruptured Aortic Aneurysm
Immediate diagnosis and surgical correction are needed to salvage patients with a ruptured abdominal aortic aneurysm. A ruptured or leaking aneurysm typically presents with back and abdominal pain and shock occurring in a middle-aged or elderly patient with known arteriovascular disease and/or hypertension. An expanding
abdomen or pulsatile abdominal mass with the loss of one or both femoral pulses completes the classic presentation. The retroperitoneal irritation produced by bleeding from an abdominal aneurysm can suggest nerve compression or a ureteral stone when it mimics “sciatica” or testicular pain. Rarely, rupture of an aortic aneurysm into the duodenum causes the massive hemoptysis of an aortoenteric fistula. (This dramatic clinical situation almost always occurs in patients with preexisting aortic grafts in place.) Unfortunately, hypotension often impedes comparison of pulse quality, and examination of the abdomen and pulses may be difficult in obese patients. Because such patients are losing “whole blood,” the hematocrit often remains stable until volume replacement is substantial or the patient nears exsanguination.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Age Predilection</th>
</tr>
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<tbody>
<tr>
<td>Appendicitis</td>
<td>Younger</td>
</tr>
<tr>
<td>Ulcer perforation</td>
<td>Younger</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>Younger</td>
</tr>
<tr>
<td>Pelvic inflammatory disease</td>
<td>Younger</td>
</tr>
<tr>
<td>Ovarian tumor</td>
<td>Older</td>
</tr>
<tr>
<td>Mesenteric ischemia</td>
<td>Older</td>
</tr>
<tr>
<td>Ruptured aortic aneurysm</td>
<td>Older</td>
</tr>
<tr>
<td>Colonic obstruction/perforation</td>
<td>Older</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>Older</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>Any age</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Any age</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>Any age</td>
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</tbody>
</table>

In recent years, dramatic advances in endovascular stenting now allow many aneurysms to be repaired without an open operative procedure. If the patient is hemodynamically stable, multiple largebore IV lines should be inserted and blood ordered before diagnostic testing. Whatever the stenting potential might be, early consultation by a vascular surgeon is indicated. A contrast CT scan and aortogram are the best tests to confirm and delineate the aneurysm in the stable patient. Ultrasonography is a quick noninvasive bedside test to confirm the presence of an aneurysm, but details of the visualization are likely to be obscured by bowel gas.
Female Pelvic Disease

Ruptured ectopic pregnancy typically presents as acute abdominal pain, hypotension, intra-abdominal or vaginal bleeding, and a palpable mass. (Acute pain occurs in almost all patients; many patients have vaginal bleeding and about half have a pelvic mass; fever is rare.) It is important to recognize that bleeding may frequently occur into the peritoneal cavity but only be appreciated with the assistance of an imaging modality or operation. A reported history of a recent menstrual period is sufficiently unreliable that it cannot be used to exclude pregnancy. Hence, a serum $\beta$-human chorionic gonadotropin (HCG) should be performed on every fertile female with acute abdominal pain. Hematocrit determinations are usually not helpful because of the acute nature of the bleeding. Ectopic pregnancy is especially likely in patients with a history of salpingitis, tubal ligation, or prior ectopic pregnancy and in patients using intrauterine devices for birth control. Young women, who are sexually active, with unexplained acute abdominal pain and shock should be considered for early laparotomy with a presumed ruptured ectopic pregnancy. (The rapid availability of US in many emergency departments and ICUs now permits confirmation of the diagnosis in less time than it takes to ready the operating room.) In patients with acute abdominal pain, stable blood pressure, and no evidence of peritoneal signs, serum pregnancy testing and ultrasonographic evaluation can be performed before surgery during initial resuscitation.

The transabdominal and transvaginal US examinations are complementary in evaluation of painful pelvic disease: lesions located “high” in the pelvis (e.g., ovarian masses) are often best seen by transabdominal screening (provided bowel gas does not obscure the view). Conversely, transvaginal scanning is often better at detecting early intrauterine pregnancy and ectopic pregnancies. Use of transabdominal or transvaginal scanning can allow detection of pregnancy at 5 weeks of gestation. The only certain US sign of ectopic pregnancy is visualizing a gestational sac outside the uterus, whereas finding a viable intrauterine pregnancy is strong evidence against a concurrent ectopic pregnancy. Ovarian tumors or cysts may also produce pelvic pain if they undergo torsion or ischemia. Rupture of a normal ovarian follicle into the peritoneum may produce worrisome but otherwise benign peritoneal signs.

Pelvic inflammatory disease (PID), the most common cause of pelvic pain in young women, is often difficult to differentiate from appendicitis or a ruptured ectopic pregnancy. PID usually starts within 7 days of the menstrual period, a helpful point in the differential with ectopic pregnancy, if the history is reliable. (The serum HCG should also be negative.) The pain of PID is gradual in onset and usually bilateral, whereas the pain of appendicitis is unilateral when fully developed. Diffuse bilateral tenderness elicited by moving the cervix during pelvic examination is key to detecting PID. The ultrasonographic and CT features of PID are subtle and nonspecific unless a frank abscess forms. Untreated, PID can progress to the formation of a pus-filled fallopian tube, that is, a tubo-ovarian abscess (TOA). TOA is an especially common problem among women with repeated or prolonged episodes of PID. Surprisingly, TOA can have such a sufficiently long time course that it can be confused radiographically with ovarian or even adjacent colon carcinoma. TOA is most frequently characterized by pelvic pain, fever and chills, and a vaginal discharge. Examination reveals lower abdominal and adnexal tenderness (usually asymmetric). Leukocytosis is a common but nonspecific finding. Both US and pelvic CT scanning are excellent for imaging the lesion. Most tubal abscesses are polymicrobial infections that include enteric aerobic Gram-negative rods, *Haemophilus*, anaerobes, and *Streptococcus*. Pelvic US or CT demonstrates an adnexal mass in more than 90% of patients. Initial management should include appropriate cultures, hemodynamic stabilization, and administration of antibiotics that cover both likely aerobes and anaerobes. (Although there are many effective options now available, a third-generation cephalosporin plus doxycycline, fluoroquinolone plus metronidazole, a second-generation cephalosporin plus doxycycline, and clindamycin plus gentamicin and metronidazole are popular, tested, and effective alternatives.)
Mesenteric Ischemia

Mesenteric ischemia afflicts the elderly, particularly those with underlying heart (e.g., congestive heart failure and atrial fibrillation) and vascular disease who develop shock. (There are now instances of mesenteric ischemia in young people resulting from cocaine-induced vasoconstriction.) The mortality of bowel infarction is high, primarily because of delayed diagnosis but also because victims tend to be older and have underlying comorbidities. The differential diagnosis includes bowel obstruction, diverticulitis, and inflammatory bowel disease.

Bowel ischemia may result from arterial or venous occlusion of the mesenteric vessels. Most vascular lesions are arterial. About 50% of patients with acute bowel ischemia have superior mesenteric artery (SMA) disease. (Half of these cases are embolic; a quarter are thrombotic, with the remainder resulting from nonocclusive ischemia.) SMA occlusion usually presents with the sudden onset of acute abdominal pain and a striking leukocytosis. Conversely, inferior mesenteric artery occlusion (accounting for about 25% of cases of bowel ischemia) usually has a more subtle, chronic pattern. The remaining 25% of cases stem from mesenteric venous thrombosis resulting from portal hypertension, pelvic infection, trauma, pancreatitis, intra-abdominal neoplasm, and thrombophilic disorders.

Arterial embolism is the single most common cause of bowel infarction and is most likely to occur among patients with atrial fibrillation or recent myocardial infarction complicated by mural thrombus. The possibility of cholesterol embolism should also be considered in patients who develop symptoms after aortic instrumentation (e.g., cardiac catheterization, aortic balloon pump). Thrombotic occlusion occurring near the aortic origin of mesenteric vessels in patients with extensive atherosclerotic disease is the second most common cause of infarction. In patients with slowly progressive occlusion, a history of “intestinal angina” caused by abdominal pain after eating, which discourages food intake, may be elicited. Vasculitis from lupus, radiation, or polyarteritis is rarely responsible. Many critically ill patients have nonocclusive bowel infarction because of the combination of hypotension and vasopressor drugs. By virtue of advanced age and atherosclerosis, many victims also have some degree of chronic vascular narrowing. (Concern over nonocclusive bowel infarction has increased recently with the resurgent use of the powerful splanchnic vasoconstrictor, vasopressin, to treat septic shock.) Initially, ischemia produces mucosal and submucosal injury and edema. Later, mucosal sloughing occurs. Unless corrected within hours, bowel necrosis and perforation result, producing generalized peritonitis.

The signs and symptoms of mesenteric ischemia are often minimal or poorly localized, although a benign abdominal exam in a patient complaining of severe abdominal pain should be a tip-off. Unfortunately, severe illness and sedation may obscure timely detection in the ICU patient. In addition, severe forms of *Clostridium difficile* colitis can be confused with mesenteric ischemia because they can present with abdominal pain, bloody stool, fever, and leukocytosis. The most common symptom of mesenteric ischemia is constant, nondiscrete back and abdominal pain. (The onset is sudden if embolic and more gradual if thrombotic or nonocclusive.) More than half of all patients have either occult blood in the stool or bloody diarrhea. Bowel sounds increase early in this process but decrease later. Shock may be the presenting symptom if perforation or infarction has already occurred. Atrial fibrillation or congestive heart failure is present in as many as half of all patients with bowel infarction.

Laboratory tests are seldom sufficiently specific or timely to define the diagnosis. Although loss of circulating volume may cause hemoconcentration, more typically, the hematocrit remains normal as the leukocyte count rises. Refractory lactic acidosis in conjunction with increased levels of potassium and phosphate is typical of infarction. Unfortunately, these abnormalities are often recognized too late to impact favorably on crucial therapeutic decisions.

Plain abdominal radiographic findings (seen in a minority of cases) include an ileus localized to the area of bowel
ischemia with dilation of large and small bowel loops and loss of haustral markings. Occasionally, gas may be seen in the portal venous system, in the bowel wall, or free in the peritoneal cavity. Hemorrhage and bowel wall edema may result in a classic “thumbprinting” pattern on the plain radiograph. CT angiography is now the diagnostic test of choice where mesenteric ischemia is a significant concern. A great advantage of CT is its simultaneous demonstration of pathology in nonvascular organs. CT of the abdomen demonstrates the suggestive findings of segmental bowel wall thickening, ascites, air in the portal vein, or focal bowel dilation with a high degree of sensitivity (approx. 85%). Occasionally, CT scan following IV contrast may directly demonstrate mesenteric vein thrombosis.

Angiography is the historical "gold standard" for diagnosis and may aid in the therapy while helping to clarify anatomic regions where CT imaging is nondiagnostic. Angiography distinguishes thrombosis and embolism from nonocclusive vasoconstriction and allows potential interventions. CT angiography, however, provides excellent detail of the vascular bed along with information on the bowel and surrounding structures. Magnetic resonance angiography (MRA), though time costly and inconvenient, may ultimately prove to be a helpful diagnostic modality because it can be performed without iodinated contrast material.

After initial stabilization with fluid and correction of electrolyte and acid-base abnormalities, cultures should be obtained and antibiotics administered to broadly cover enteric pathogens. In patients with peritoneal signs and those with CT or angiographic findings indicative of intestinal perforation or infarction, immediate surgery should be undertaken. At the time of surgery, nonviable segments of bowel should be removed. A "second-look" operation 24 to 36 hours following revascularization is often advisable to allow dying tissue time to demarcate.

In patients with symptoms of short duration suggesting that infarction has not yet occurred, CT or angiographic diagnosis followed by heparin anticoagulation and correction by surgery or interventional radiographic technique is as likely to result in a good outcome. For example, direct mesenteric artery infusion of papaverine may improve the perfusion of nonocclusive ischemic gut, delaying or averting surgery. If clot is found, catheter embolectomy or thrombolytic infusion may be helpful. For patients found to have focal arterial narrowing, angioplasty with stent placement may be useful, although surgical revascularization is still preferred for nonembolic occlusions. Regardless of etiology, prognosis is best when revascularization is performed on a “nonsurgical” abdomen. Unfortunately, the diagnosis of ischemic bowel disease is often overlooked or delayed until the clinical condition has deteriorated too far to permit salvage.

**Appendicitis**

The demographics and management strategies for appendicitis are in the process of evolution. Historically, appendicitis was a disease much more commonly seen in the first three decades of life than among older patients. Appendicitis is now seen in all age groups. (Appendicitis is the most common surgical issue encountered during pregnancy.) Early diagnosis is critical to prevent the major complications of perforation, abscess formation, and severe sepsis. The classic features of acute appendicitis—midepigastric pain migrating to the right lower quadrant accompanied by nausea and vomiting—are seen in less than half of all ambulatory patients and probably even fewer critically ill patients. The site of pain is not predictable because of the variable location of the cecum and appendix. Appendicitis is often overlooked in the absence of fever, leukocytosis, a localizing physical examination, or a “classic” history. Physical examination usually reveals a mildly elevated temperature with moderate acute abdominal pain. Generalized peritoneal signs are absent until perforation has occurred. Pelvic and rectal examinations are particularly helpful in localizing the pain to the right lower quadrant and excluding alternative diagnoses. Laboratory examination is nonspecific; a mildly elevated WBC count is seen in about 70% of patients. Urinalysis and a pregnancy test should be performed to inappropriate patients to help
exclude alternative diagnoses. However, up to one third of patients with appendicitis will have microscopic hematuria and pyuria. The plain radiograph is not usually helpful. (Even when perforation is demonstrated surgically, free intra-abdominal air is only seen radiographically in half of all patients.) CT scanning is now more than 95% sensitive and specific. If an air- or contrast-filled appendix is seen, the diagnosis is all but excluded. Alternatively, discovery of a mass or fat stranding in the cecal region, edema or thickening of the appendiceal wall, or an appendicolith is highly suggestive of appendicitis. If the diagnosis is missed, the delayed supplicative complications are easily diagnosed by CT. US is probably not as useful as CT for diagnosis but is an excellent tool to exclude alternative causes of abdominopelvic pain in women.

Treatment of uncomplicated acute appendicitis (i.e., symptoms <72 hours without evidence of perforation) is surgical removal after prompt correction of any significant fluid or electrolyte abnormalities. For many noncritically ill patients, laparoscopic appendectomy permits rapid hospital discharge. (Antibiotic therapy beyond that routinely used for surgical prophylaxis is unnecessary.) Increasing attention is now being paid to managing episodes of uncomplicated appendicitis solely with antibiotic therapy. Data on long-term outcomes with this strategy, however, are not available. It is not uncommon for patients to have a recurrent episode of appendicitis. Repeated exposure to broad-spectrum antibiotics is also a concern as resistant organisms may be selected. If diagnosis is delayed and perforation with abscess formation has occurred, there is general agreement that antibiotics and percutaneous drainage of any abscess, followed by surgical intervention after the patient has stabilized, are warranted. Patients with symptoms of 2 to 5 days in duration without clear evidence of perforation should probably be operated on, as should those with coexisting intestinal ischemia or other life-threatening abdominal process.

Pancreatitis

Etiology

Cytotoxic effects of alcohol- and gallstone-induced reflux of bile into the pancreatic duct account for nearly 80% of all cases of acute pancreatitis. Ethanol is a more likely etiology in men, whereas gallstones are a more frequent cause in women. Other causes include trauma, tumors, medications, electrolyte disturbances, toxins, infections, and surgery (Table 36-3). Gallstones that precipitate acute pancreatitis usually affect the ampulla of Vater. Patients with biliary tract obstruction complicating gallstone pancreatitis may present concurrent biliary tract infection (cholangitis), a complication that raises mortality risk dramatically. Two thirds of patients with gallstone pancreatitis who defer stone removal experience symptom recurrence. Tumors of the pancreas and common bile duct or ampullary stenosis after biliary tract surgery also may induce pancreatitis by obstructing the free flow of bile. Visualization of the pancreatic duct by endoscopic retrograde cholangiopancreatography (ERCP) often reveals structural abnormalities, tiny stones, or thick biliary sludge that helps explain recurrent pancreatitis of obscure etiology. The ERCP procedure itself may elevate serum amylase; however, most of these cases are asymptomatic.

Ethanol leads the list of toxins and medications that commonly cause acute pancreatitis. Other direct pancreatic toxins include methanol, carbon tetrachloride, and organophosphate insecticides. Numerous medications have been implicated in causing acute pancreatitis, but a diagnosis of druginduced pancreatitis is always suspected, and it is believed that drugs account for less than 1% of all cases (Table 36-4). The one group of patients in whom drug-induced pancreatitis is common are patients with HIV infection taking antiretrovirals. In lipid-induced acute pancreatitis, triglyceride levels usually exceed 1,000 mg/dL. The diagnosis often is difficult to make because triglycerides interfere with assays of serum amylase and frequently are elevated, even when acute pancreatitis has another cause. Hypercalcemia-induced acute pancreatitis may occur in association with untreated hyperparathyroidism. Pancreatitis also is seen in patients undergoing solid organ transplantation,
possibly because of the use of cyclosporine for immunosuppression.

Table 36-3. Causes of Acute Pancreatitis

<table>
<thead>
<tr>
<th>Causes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common causes (approx. 80%)</strong></td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td></td>
</tr>
<tr>
<td>Gallstones</td>
<td></td>
</tr>
<tr>
<td><strong>Less common causes (approx. 15%)</strong></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
</tr>
<tr>
<td>Drug-induced</td>
<td></td>
</tr>
<tr>
<td>Abdominal trauma</td>
<td></td>
</tr>
<tr>
<td><strong>Rare causes (approx. 5%)</strong></td>
<td></td>
</tr>
<tr>
<td>Biliary ascariasis</td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia/hyperparathyroidism</td>
<td></td>
</tr>
<tr>
<td>End-stage renal failure</td>
<td></td>
</tr>
<tr>
<td>Penetrating duodenal ulcer</td>
<td></td>
</tr>
<tr>
<td>Organ transplant associated</td>
<td></td>
</tr>
<tr>
<td>Pancreas divisum</td>
<td></td>
</tr>
<tr>
<td>Ampullary stenosis or spasm</td>
<td></td>
</tr>
<tr>
<td>Hereditary</td>
<td></td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td></td>
</tr>
<tr>
<td>Viral infections (CMV; mumps; hepatitis A, B, and C; EBV)</td>
<td></td>
</tr>
<tr>
<td>AIDS-associated</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
</tr>
</tbody>
</table>

Some combination of direct cytotoxic injury, ductal obstruction, and bile and duodenal reflux initiates pancreatic injury. Regardless of the inciting stimulus, the subsequent pancreatitis results from organ damage caused by autodigesting enzymes. Trypsin and chymotrypsin, lipase, and elastase are responsible for damage to proteins, lipids, and elastin, respectively. Trypsin is not only destructive to proteins but also a potent activator of other proenzymes. Trypsin-induced activation of phospholipase A and the kinin-kallikrein system probably is responsible for many of the hemodynamic and vascular permeability changes associated with pancreatitis. Enzyme-induced inflammation disrupts pancreatic ducts, breaks down vessel walls, causes fat necrosis, and kills both exocrine and endocrine pancreatic cells. Enzymatic injury is accompanied by a marked infiltration of inflammatory cells including macrophages, lymphocytes, neutrophils, and monocytes, which release a host of inflammatory mediators including proinflammatory cytokines, prostaglandins, and leukotrienes. The most severe cases of necrotizing pancreatitis are accompanied by hemorrhage. With the exception of alcohol-induced pancreatitis, most cases (>80%) are self-limited, leaving little residual pancreatic damage. Only rarely does acute pancreatitis progress to a chronic form.
### Table 36-4. Implicated in Causing Pancreatitis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td>Asparaginase</td>
<td>Azathioprine</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Danazol</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Ergotamine</td>
</tr>
<tr>
<td>Diphenoxylate</td>
<td>Ethacrynic acid</td>
</tr>
<tr>
<td>Estrogens</td>
<td>Gold compounds</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Isotretinoin</td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>Methyldopa</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>Ranitidine</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Sulindac</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Thiazides</td>
</tr>
<tr>
<td>Valproic acid</td>
<td></td>
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</tbody>
</table>

### Diagnosis

Patients with pancreatitis usually present with severe, constant, “boring” abdominal, and/or back pain made worse by lying supine. Nausea, vomiting, and low-grade fever are common. However, less-than-typical acute presentations (chest pain, shock, respiratory distress, etc.) often are encountered. Occasionally, presenting signs of pancreatitis in the ICU patient are subtle. Tube feeding intolerance, hypocalcemia, or an unexplained fever or decline in hematocrit may be the only manifestations, especially in patients with impaired mental status. Pancreatitis can be difficult to distinguish from cholecystitis, mesenteric ischemia, ulcer disease (especially posterior duodenal ulcers), and diverticular inflammation. Tachycardia is nearly universal because of pain and intravascular volume depletion. Volume depletion often
produces hypotension. Epigastric tenderness with or without signs of peritoneal irritation is the most common finding on physical examination. (Rebound tenderness is not common because of the retroperitoneal location of the gland.) Pain often is worse when the patient is supine. Chest examination may reveal rales characteristic of atelectasis or acute lung injury. Bluish discoloration of the flanks (Grey-Turner sign) or periumbilical region (Cullen sign) is a rare manifestation of retroperitoneal hemorrhage. Red subcutaneous nodules of fat necrosis and hypocalcemic tetanus are extremely rare.

Leukocyte counts commonly range from 10,000 to 25,000 cells/mm$^3$. Volume depletion frequently causes elevation of the blood urea nitrogen and hemoconcentration; later, anemia is the rule. Increased levels of stress hormones (glucagon, cortisol, and epinephrine) often produce hyperglycemia. Increased capillary permeability and chronic illness (especially alcoholism) commonly cause hypoalbuminemia. Transient hypertriglyceridemia and mild elevations in hepatic transaminase also are seen frequently.

Plasma amylase and lipase are the two enzymes most frequently assayed to diagnose pancreatitis. Unfortunately, many conditions not associated with acute pancreatitis elevate the amylase level, making this test much less specific than commonly perceived (Table 36-5). For example, as many as one third of all patients undergoing laparotomy and nearly one fourth of those having major extraabdominal surgery have elevated amylase levels without pancreatic manipulation or clinical evidence of pancreatitis. The specificity of amylase for diagnosing acute pancreatitis can be improved by using a cutoff of two to five times the laboratory upper limit of normal; however, the degree of serum amylase elevation has no prognostic value. Amylase determinations also lack sensitivity. Because amylase peaks within 24 hours of disease onset and then declines gradually, as many as one third of patients with clinical and radiographic features of acute pancreatitis have unimpressive serum amylase values when first seen. High rates of false-positive and false-negative results limit the clinical utility of amylase clearance tests. (e.g., renal failure is one of many conditions that increase the ratio of amylase clearance to creatinine clearance.) Lipase is more specific than amylase as an indicator of pancreatitis. Lipase peaks even later and clears more slowly than amylase, remaining elevated for up to 14 days. Therefore, it can help in making a diagnosis in a patient who presents late in the course of disease. Unlike amylase, lipase rarely is elevated in patients with burns, diabetic ketoacidosis, pelvic infection, salivary gland dysfunction, or macroamylasemia but, like amylase, may be elevated in renal failure.

Table 36-5. Nonpancreatic Causes of Amylase Elevation

<table>
<thead>
<tr>
<th>Alcoholism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal trauma</td>
</tr>
<tr>
<td>Macroamylasemia</td>
</tr>
<tr>
<td>Perforated duodenal ulcer</td>
</tr>
<tr>
<td>Mesenteric ischemia</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
</tr>
<tr>
<td>Morphine administration</td>
</tr>
<tr>
<td>Lung cancer</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
</tr>
<tr>
<td>Gallbladder disease</td>
</tr>
<tr>
<td>Hepatic failure</td>
</tr>
</tbody>
</table>
The chest radiograph commonly demonstrates nonspecific bibasilar atelectasis, diaphragmatic elevation, or pleural effusion. Diffuse infiltrates suggest acute respiratory distress syndrome (ARDS). Abdominal films are never diagnostic but may reveal the suggestive signs of localized ileus, such as “the colon cutoff sign” or the “sentinel loop.” Free air may enter the abdomen in patients with pancreatitis resulting from ulcer perforation. A “soap bubble” appearance of the pancreatic bed, calcifications suggestive of chronic pancreatitis, and obscured psoas margins are other clues.

Abdominal US is a useful bedside screening test for many patients with abdominal pain, but suboptimal visualization of the pancreas occurs in many patients because of obesity or excessive bowel gas from the accompanying ileus. US is good at detecting gallstones and biliary duct dilation and for observing the course of pancreatic pseudocysts but is inferior to CT for detecting or staging pancreatitis and most of its complications. CT scanning is the single best test to visualize the pancreas because it is unaffected by patient size or the presence of bowel gas. CT scanning demonstrates some radiographic abnormality in two thirds of all patients with pancreatitis (pancreatic edema or necrosis or peripancreatic fluid collections) and is abnormal in all patients with severe disease but provides an etiologic diagnosis less frequently. To obtain data about pancreatic viability, rapid phase contrast scanning must be performed. Unfortunately, many patients with pancreatitis have elevated creatinine, which raises questions about the safety of intravenous contrast. Pancreatic necrosis appears as areas of low to no enhancement on CT scanning because of disruption of the pancreatic microcirculation. As more of the pancreas becomes necrotic, the accuracy of CT in diagnosing necrotizing pancreatitis increases significantly. Infection of the necrotic tissue is diagnosed via CT-guided or ultrasound-guided fineneedle aspiration of the tissue, followed by culture and Gram stain. Of the available options to obtain diagnostic specimens of fluid associated with pancreatitis, CT-guided aspiration is preferred because it has higher sensitivity and specificity versus other modalities.

In addition to confirming the diagnosis, CT scan-based scoring systems have been developed for assessing severity, as exemplified in Table 36-6. In the system illustrated, the presence of pancreatic enlargement, surrounding inflammation, peripancreatic fluid collections, and pancreatic necrosis correlates inversely with prognosis. CT scanning is prognostically useful but has its greatest value in documenting the late complications of peripancreatic fluid accumulation, pseudocyst formation, necrosis, and abscess development and drainage. Diagnostic CT-directed aspiration is useful to establish infection and in many cases to initiate drainage of mobile pancreatic fluid. Percutaneous aspiration fails when the fluid is extremely viscous or cannot be approached safely because of its location.

Because ERCP can exacerbate acute inflammation and cause infection, it probably should be reserved for cases where aberrant ductal anatomy is suspected, trauma-induced pancreatitis where ductal integrity is in question, or acute stone extraction (gallstone-induced pancreatitis) is anticipated. In traumatic cases, ERCP visualizes the damaged pancreatic duct, helping plan the repair. In moderate to severe cases of gallstone-induced pancreatitis, ERCP permits stone extraction and reduces hospital stay, complications, and mortality. However, extraction must occur early in the course of symptoms to abort a full-blown attack. ERCP also is useful in the first episodes of pancreatitis for patients older than 40 years of age, in whom ampullary tumors and pancreas divisum are more common findings.

Table 36-6. CT Scan Assessment of Severity
**CT Characteristics**

<table>
<thead>
<tr>
<th>CT Characteristics</th>
<th>Grade of Acute Pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal pancreas</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatic enlargement</td>
<td>1</td>
</tr>
<tr>
<td>Inflammation of the pancreas and peripancreatic fat</td>
<td>2</td>
</tr>
<tr>
<td>One fluid collection or phlegmon</td>
<td>3</td>
</tr>
<tr>
<td>Two or more fluid collections</td>
<td>4</td>
</tr>
</tbody>
</table>

**Degree of pancreatic necrosis**

| Necrosis of one third of pancreas                        | 2                          |
| Necrosis of one half of pancreas                          | 4                          |
| Necrosis of more than one half of pancreas                | 6                          |

**Total score**

| Total score                                              | 0-10                       |

**Prognosis**

As with other critically ill patients, prognosis is determined largely by the number and severity of organ system failures. Severity of illness can be assessed by simply counting the number of failing organ systems or by using a more formal scoring system, such as the APACHE score. Prognostication in pancreatitis has been studied extensively, and certain specific clinical features have been integrated to form the predictive Ranson and Glasgow Scales (Table 36-7). These two clinical scales are used in addition to the CT-based scoring systems outlined earlier. Patients with fewer than three of the Ranson criteria generally fare well. A simplified Glasgow Scale has been developed along similar lines. Of all clinical features, pancreatic necrosis with hemorrhage carries the worst prognosis. Severe acute pancreatitis progresses to necrotizing pancreatitis in approximately 15% of patients. Infected pancreatic necrosis occurs in 30% to 70% of patients with necrotizing pancreatitis and increases mortality risk relative to sterile collections. Death from alcohol-induced pancreatitis usually occurs early in the hospital course, often as a result of hypovolemia, whereas death from gallstone-induced pancreatitis usually occurs later, as a result of severe sepsis originating in devitalized hemorrhagic pancreatic tissue. The long-term outcome from pancreatitis is good, provided that causative gallstones are extracted and alcohol is avoided. Unless extensive necrosis occurs, survivors of a single episode rarely have either endocrine or exocrine pancreatic insufficiency.
### Table 36-7. Adverse Prognostic Features of Acute Pancreatitis

<table>
<thead>
<tr>
<th>Ranson Criteria</th>
<th>Simplified Glasgow Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;55 years</td>
<td>Age &gt;55 years</td>
</tr>
<tr>
<td>Calcium &lt;8 mg/dL</td>
<td>Calcium &lt;8 mg/dL</td>
</tr>
<tr>
<td>Glucose &gt;200 mg/dL</td>
<td>Glucose &gt;180 mg/dL</td>
</tr>
<tr>
<td>ARDS</td>
<td>PaO₂ &lt; 60 mm Hg</td>
</tr>
<tr>
<td>WBC &gt; 16,000/mm³</td>
<td>WBC &gt; 15,000/mm³</td>
</tr>
<tr>
<td>Rise in BUN &gt; 5 mg/dL</td>
<td>BUN &gt; 45 mg/dL</td>
</tr>
<tr>
<td>SGOT or LDH &gt; 350 units/dL</td>
<td>LDH &gt; 600 units/L</td>
</tr>
<tr>
<td>Falling hematocrit</td>
<td></td>
</tr>
<tr>
<td>Albumin &lt;3.2 g/dL</td>
<td></td>
</tr>
<tr>
<td>Base deficit &gt;4 mEq/L</td>
<td></td>
</tr>
<tr>
<td>Repletion volume &gt;6 L</td>
<td></td>
</tr>
</tbody>
</table>

ARDS, acute respiratory distress syndrome; BUN, blood urea nitrogen; LDH, lactic dehydrogenase; SGOT, serum glutamic-oxaloacetic transaminase; WBC, white blood cells.

### General Care

Treatment of pancreatitis remains largely supportive. Because marked reductions in circulating volume are common, early, adequate fluid resuscitation remains key to initial management. Unfortunately, the optimal guiding parameters for resuscitation (e.g., central vascular ultrasound, CVP, or lactate) and their specific target values remain undecided. Regardless of the method of monitoring, 5 to 10 L of crystalloid is often required early in the first day of the disease. Common causes of hypovolemia include extravascular (third space) losses into the pancreas and retroperitoneum, intraluminal gut sequestration (because of ileus), and vomiting.

Current evidence does not support prophylactic antibiotic use in patients with acute pancreatitis. Evidence of infected pancreatic tissue, sepsis, and systemic inflammatory response are indicators for therapeutic antimicrobial intervention. Elevated lactate dehydrogenase concentrations, low PaO₂, high CT severity scores, and delayed fluid resuscitation have been loosely associated with an increased risk of infection. Pathogens pass easily between the nonencapsulated pancreas and other abdominal organs. If sepsis is likely, early administration of broad-spectrum antibiotics is recommended to reduce mortality, based on data indicating that lack of appropriate antimicrobial administration results in a significant increase in mortality in septic shock.
Broad-spectrum antibiotics should be adjusted and therapeutic spectrum narrowed based on culture and susceptibility results. Failure to narrow antibiotic spectrum has resulted in an increased incidence of multidrug-resistant organisms and fungal infections within pancreatic tissue. Fine-needle aspiration may be useful in patients with signs of sepsis but equivocal findings of infected pancreatic necrosis on diagnostic imaging. Determination of pathogen(s) helps de-escalate antimicrobial therapy for infected pancreatic necrosis.

**Nutrition**

In patients with mild pancreatitis, regular oral intake may resume with symptomatic improvement or when patients are subjectively hungry. Patients with moderate or severe pancreatitis may not be able to tolerate adequate oral nutrition for an extended period. Thus, after initial resuscitation, early nutritional support should be considered for those with a functioning bowel. Current evidence demonstrates the desirability of using the enteral versus parenteral route for nutrition. Improved outcomes have been demonstrated with enteral nutrition regarding organ dysfunction, infectious complications, and mortality. Early (as opposed to delayed) initiation of parenteral nutrition tends to increase complications. Parenteral nutrition should be restricted to those patients unable to tolerate the enteral route because of ileus or those who encounter worsening symptoms during an enteral feeding trial.

There is little evidence to differentiate between the efficacies of gastric and jejunal enteral nutrition. Although concerns for aspiration, worsening of abdominal pain, or diarrhea have been raised, these complications do not appear to be significantly more common with gastric feeding. In patients with evidence of gastric outlet obstruction or in those who do not tolerate gastric feeding, there may be benefit from jejunal access for enteral nutrition delivery.

**Procedures**

The clearest indication for early procedural intervention is obstructive choledocholithiasis. The mortality rate from untreated gallstone-induced pancreatitis is dramatically reduced by early intervention. If extraction can be accomplished soon after presentation, endoscopic stone removal is effective in aborting pancreatitis, improving survival, and reducing infectious complications in patients with moderate to severe disease. Ideally, the gallbladder may be removed during the same hospitalization to eliminate the source of stones. Even though most cases of gallstone-induced pancreatitis will resolve spontaneously, removal of residual stones and the gallbladder dramatically reduces the risk of recurrence. Liberal use of CT scanning has made diagnostic uncertainty an uncommon reason to go to the operating room. Late complications including nonresolving pseudocyst, infected pancreatic necrosis, fistula formation, and pancreatitis-induced hemorrhage also are valid procedural indications. Because pancreatectomy carries a high mortality and does not reduce the incidence of complications, it has been abandoned as a therapy for acute pancreatitis. It is rare that a single operation is sufficient for the complicated case of pancreatitis; multiple trips to the operating suite are often needed for a satisfactory outcome.

Based on available evidence, a “step-up” approach to management of pancreatitis complicated by necrosis has been developed. This strategy begins with less invasive techniques and progressively escalates for treatment failure. Percutaneous drain placement is often the first approach. Endoscopic techniques are either applied initially or as the next step after percutaneous strategies. Endoscopic transluminal drainage may be conducted through the duodenum or stomach. Minimally invasive surgery directed at the retroperitoneum may follow as the next step, if necessary. In general, surgical or endoscopic pancreatic debridement or drainage is now only required with lack of clinical resolution of symptoms and is delayed until pancreatic necrosis has become walled off. A growing body of evidence supports minimally invasive
techniques and delaying or even avoiding major surgical procedures in patients with pancreatitis progressing to necrosis.

Complications

Infectious complications and multiple organ failure are the most frequent cause of death in pancreatitis. Common infections include pancreatic or subdiaphragmatic abscess, cholangitis, and peritonitis. A variety of Gram-positive and Gram-negative organisms may be found in pancreatic infections (Table 36-8). Hypoxemia occurs in as many as two thirds of all patients with pancreatitis; one in three patients develops infiltrates, atelectasis, or pleural effusions.

Hydrostatic pulmonary edema frequently complicates excessive fluid replacement. Although pleural effusions usually are exudative in character, left-sided, bilateral, or right-sided effusions are possible. If suspicious, effusions should be tapped to exclude the possibility of empyema, particularly if fluid appears suddenly or late in the clinical course. Pneumonia occurs frequently and fat embolism is not rare. ARDS, the most feared complication, occurs in 10% to 20% of cases, usually in patients with severe disease. The etiology of ARDS is unknown but possibly relates to the circulatory release of inflammatory mediators. The ventilator management of pancreatitis-induced ARDS does not differ from that of ARDS of any other cause and should include reduced tidal volume ventilation to limit alveolar distention.

Table 36-8. Bacteria Recovered in Pancreatic Infections

<table>
<thead>
<tr>
<th>Bacteria</th>
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<tbody>
<tr>
<td>Escherichia coli</td>
</tr>
<tr>
<td>Pseudomonas species</td>
</tr>
<tr>
<td>Mixed anaerobic infections</td>
</tr>
<tr>
<td>Staphylococcus</td>
</tr>
<tr>
<td>Klebsiella species</td>
</tr>
<tr>
<td>Proteus species</td>
</tr>
<tr>
<td>Streptococcus</td>
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<tr>
<td>Enterobacter species</td>
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Pancreatic inflammation commonly activates the coagulation cascade, but clinical evidence of coagulopathy is unusual. Although bleeding is more common than inappropriate clotting, splenic or portal vein thrombosis may complicate acute pancreatitis. A variety of fluid and electrolyte disorders occur commonly in acute pancreatitis (see Chapter 13). Total and ionized calcium levels usually reach their nadir approximately 5 days after pain begins. Even though biochemical hypocalcemia is frequent and may persist for weeks, related symptoms are rare. Mechanisms include the formation of intra-abdominal calcium complexes, hypoalbuminemia, and increased release of glucagon or thyrocalcitonin. Treatment parallels that of any case of symptomatic hypocalcemia. Serum magnesium may be reduced by vomiting, diarrhea, poor oral intake, or deposition in necrotic fat. Hypomagnesemia, especially common in alcohol-induced acute pancreatitis, may precipitate refractory hypokalemia and hypocalcemia.

Pancreatic inflammation and pseudocysts can erode into major vessels, resulting in massive hemorrhage into the GI tract, peritoneal cavity, or retroperitoneum. Vascular erosion presumably is due to the effects of proteolytic enzymes and direct pressure necrosis in the case of pseudocysts. Patients developing pancreatitis are prone to develop other GI hemorrhage problems, including gastric stress ulceration, peptic
ulcer disease, variceal bleeding, and splenic vein thrombosis. Patients who bleed into the pancreatic parenchyma a condition known as hemorrhagic pancreatitis have a greater mortality risk. Hemorrhagic pancreatitis has no distinctive clinical features. Coagulation disorders that accompany acute pancreatitis worsen the hemorrhagic tendency, regardless of the bleeding source.

Oliguric acute kidney injury occurs in approximately 25% of all patients with pancreatitis. Hypovolemia, hypotension, sepsis, IV contrast, and drug-induced renal damage are the most frequent causes. Acute pancreatitis can produce ascites when transudative fluid crosses the retroperitoneal boundary or when ductal disruption causes spillage into the peritoneum. When pancreatic secretions leak into the peritoneal cavity, intense inflammation causes massive exudation (pancreatic ascites). Pressure high enough to cause ACS may result. Overt disruption of the pancreatic duct commonly accompanies traumatic or hemorrhagic acute pancreatitis. When ductal disruption occurs, amylase levels in ascitic fluid typically exceed the corresponding serum levels, often rising to higher than 1,000 IU/L. Prolonged nutrition support and drainage may be required for resolution of the ascites. Surgical treatment is indicated in refractory cases and should be guided by preoperative ERCP.

Pancreatitis is associated with a variety of complications including pseudocyst, phlegmon, abscess, fistula, and chronic pancreatitis (Table 36-9). Pseudocysts, focal collections of fluid, form in about one half of all cases of acute pancreatitis and frequently present within the first weeks of illness. Pseudocysts are most commonly associated with severe cases of acute pancreatitis. Initial detection is by abdominal imaging, generally with CT. Luckily, one half of all pseudocysts resolve promptly. In the remainder, 6 months or longer may be required for spontaneous resolution. Because pseudocyst drainage or excision often proves difficult, operative intervention should only be considered for those with acute complications or persistent, incapacitating symptoms. A drop in hematocrit with signs of shock and abdominal distention is a reason for immediate intervention. A phlegmon with solid masses of indurated pancreas that may be detected as an abdominal mass by CT scanning. Phlegmon should be suspected in patients with persistent fever, abdominal pain, and tenderness, especially if leukocytosis persists. Many phlegmons resolve spontaneously within 10 to 14 days. Pancreatic abscess is a poorly defined term applied to a variety of necrotic pancreatic tissue collections. The current, more descriptive terminology for this problem is “infected necrotic pancreatitis.” Infected necrosis is uncommon, occurring in only 1% to 10% of all cases, but occurs with higher frequency in clinically severe cases, especially those resulting from biliary tract obstruction. Infection forms in the pancreatic bed late in the course (typically after 3 to 4 weeks of illness). Slightly more than one half of infected peripancreatic collections are polymicrobial, with a predominance of enteric Gram-negative rods. Surgical or catheter drainage and culture-directed antibiotics are indicated in such cases. By locally invasive autodigestion, acute pancreatitis can lead to the formation of fistulas. Fistulas, although rare, may connect the pancreas to the colon, stomach, duodenum, bile duct, small bowel, or skin surface. Repeated bouts of acute pancreatitis may produce chronic pancreatitis, a disease characterized by recurrent pain of varying intensity and deficiency of endocrine and exocrine pancreatic function (diabetes and malabsorption).

<table>
<thead>
<tr>
<th>Table 36-9. Regional Complications of Pancreatitis</th>
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<tbody>
<tr>
<td><strong>Acute</strong></td>
</tr>
<tr>
<td>Necrosis</td>
</tr>
<tr>
<td>Infected necrosis</td>
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Abdominal Compartment Syndrome

Significant increases in intra-abdominal pressure because of ascites, pancreatitis, hemoperitoneum, retroperitoneal hemorrhage, severe gut edema, or intestinal obstruction can lead to important physiological derangements (see Chapter 35). High abdominal pressure forces the diaphragm cephalad, promoting basilar atelectasis and restricting ventilation. By decreasing visceral organ perfusion, ACS causes oliguria, impaired liver and bowel perfusion, and decreased venous return. Bacterial translocation or frank bowel wall ischemia may supervene. Such findings are particularly common among patients with shock. In addition, pressure-induced cephalad movement of the diaphragms decreases thoracic compliance and impairs gas exchange. Intra-abdominal pressures are commonly and most precisely estimated by instilling 25 mL of sterile fluid into the bladder via a Foley catheter and measuring the resulting pressure. When pressures exceed 20 mm Hg in the presence of worrisome laboratory and compatible clinical deterioration, decompressive paracentesis or laparotomy should be strongly considered. The threshold for intervention should take into account the mean arterial pressure and the pressure difference driving perfusion. (Like cerebral perfusion pressure, abdominal perfusion pressure can be calculated as the difference between mean arterial pressure and abdominal pressure.)

Cholecystitis and Cholangitis

Presentation

Among ambulatory patients, more than 90% of cases of cholecystitis result from obstruction of the cystic duct by gallstones. In this group, the disease spontaneously remits as the stone moves from the cystic duct orifice and swelling resolves. If a stone obstructs the common bile duct, spontaneous resolution is much less probable. Symptoms frequently progress when pancreatitis, cholangitis, gangrene of the gallbladder, or emphysematous cholecystitis complicates cholecystitis. Emphysematous cholecystitis (gas in the wall of the gallbladder) is an inflammatory complication of cholecystitis occurring most often in diabetics and immunocompromised patients. Acalculous cholecystitis occurs more frequently than stone-caused disease in hospitalized persons.
mechanism(s) by which inflammation and necrosis of the gallbladder occur in the absence of stones is unknown. However, bile stasis seems likely to play an etiologic role because acalculous cholecystitis tends to occur in patients deprived of the oral alimentation that produces the normal pattern of phasic gallbladder emptying. Bacteria play a minor (if any) causative role in the development of typical cholecystitis, which is generated predominantly by mechanical occlusion of the cystic duct by a stone in a younger patient. By contrast, cholangitis arises primarily in elderly patients and occurs when bacteria reflux into a partially obstructed biliary duct, producing infection. Life-threatening sepsis may result as infected bile, under pressure, seeds the bloodstream with bacteria and their inflammatory by-products. Cholangitis and cholecystitis are most common among patients with gallstones, previous biliary surgery, pancreatic or biliary tumors, or other obstruction to bile flow.

The signs and symptoms depend on whether simple cholecystitis is present or a complication has occurred (e.g., cholangitis). With both conditions, epigastric and right upper quadrant pain are typical and may radiate to the shoulder. The pain is usually described as deep and gnawing but may be sharp in character. Jaundice is variably present, and nausea and vomiting are typical but nonspecific signs. Physical examination reveals right upper quadrant tenderness and guarding. A mass is palpated in the right upper quadrant in about 20% to 30% of patients. Physical findings of generalized peritonitis are rare and should suggest a complication (e.g., ruptured gallbladder) or another diagnosis (e.g., perforated ulcer). When cholangitis is present, the physical findings are referred to as either a classic triad or pentad. The triad (fever, chills, and right upper quadrant pain) is seen in 70% of patients; addition of mental status changes and septic shock completes a pentad seen in another 10%.

**Diagnosis**

The leukocyte count is elevated (at times exceeding 15,000 cells/mm$^3$) in about two thirds of patients with cholecystitis. Even when the total WBC count is normal, granulocytes usually predominate. Higher leukocyte counts suggest cholangitis. The bilirubin is elevated in 80% of cases of acute cholecystitis, but in most cases, it remains under 6 mg/dL. (A bilirubin >4 mg/dL is suggestive of a common bile duct stone.) The alkaline phosphatase is usually modestly elevated (<2 to 3 times normal) unless obstruction is severe or prolonged. Serum levels of liver transaminases are usually only modestly elevated. A low-grade coagulopathy is common, manifested as a decreased platelet count and prolonged prothrombin time. The serum amylase may be modestly elevated even in the absence of pancreatitis.

Plain radiographs visualize only 15% to 20% of gallstones. If gas is seen in the biliary tract, it is virtually diagnostic of cholangitis unless the patient is post ERCP, has had prior biliary duct surgery, or in the setting of intestinal ischemia. US will visualize gallstones and dilated biliary ducts reliably if sufficient time has elapsed for ductal distention to occur. US cannot reliably make the diagnosis of simple acute cholecystitis, but gallbladder enlargement, wall thickening, and edema are suggestive. Occasionally, US discloses edematous changes within the pancreas suggestive of gallstone-induced pancreatitis. Typical patients with acalculous cholecystitis do not have evidence of gallstones or sludge but often have a thickened gallbladder wall (>5 mm) with pericholecystic fluid. In summary, US is sensitive and specific for gallstones but cannot be diagnostic for cholecystitis unless ductal dilation, gross wall thickening, perforation, or gas in the gallbladder wall is detected. In critically ill patients with an acute abdomen, early operative intervention is probably indicated regardless of US findings.

Among stable patients in whom there is diagnostic uncertainty after US, the CT scan and nuclear biliary scans may be helpful. CT scanning may be a superior method of demonstrating dilated intrahepatic channels and processes in the region of the common bile duct, but the portability of US makes it the procedure of first choice. Occasionally, thin-cut CT scanning will detect biliary tract stones missed by US
because of its high resolution and superior ability to detect calcification. On CT, acute cholecystitis is indicated by gallbladder enlargement (>5 cm) and wall thickening (>3 mm). The rare occurrence of emphysematous cholecystitis is also easily seen by CT. Finally, the CT scan is also useful to find other intra-abdominal conditions that can be confused with cholecystitis that are poorly detected by US.

Nuclear biliary scans may also be used to evaluate the function of the liver and biliary tract. A radioactive analog of HIDA is administered, taken up by the liver, and secreted into the bile, where it outlines the major intrahepatic ducts, gallbladder, and common bile duct. The gallbladder should demonstrate uptake within 30 to 60 minutes if normal. Delayed imaging at 4 hours that fails to visualize the gallbladder is highly suggestive of acute cholecystitis. Nonvisualization of the gallbladder is common in patients with cystic or common duct obstruction, but nonvisualization may also occur with starvation, pancreatitis, perforated peptic ulcer, TPN use, and severe hepatic dysfunction. The specificity of nonvisualization on biliary scan is high (>90%) if gallstones are present, but in acalculous cholecystitis, the specificity falls to about 40%. It is important not to let the inherent delays imposed by HIDA scanning postpone laparotomy if it is emergently necessary.

**Management**

ERCP requires a skilled operator and transport of a relatively stable patient to the radiology suite. This technique, however, allows direct visualization of the ampulla and radiographic visualization of the intrahepatic and pancreatic ducts—information that is helpful when malignancy is suspected. ERCP also offers the option of stone extraction or dilation of a stenotic ampulla.

In many patients, cholecystitis resolves spontaneously. However, even when the disease worsens, frank cholangitis is not seen until more than 48 hours following ductal obstruction. Intraoperative bile cultures are positive in the majority of patients; two or more organisms are commonly recovered. Although the most common organisms are *Escherichia coli*, *Klebsiella* species, and *Streptococcus faecalis*, anaerobes (i.e., *Bacteroides fragilis* and *Clostridium perfringens*) are isolated in about 40% of infected patients.

Patients with cholecystitis or cholangitis should be stabilized hemodynamically, cultured, and given analgesics. Feeding should be withheld. Although antibiotic use for uncomplicated cholecystitis is controversial, as a practical matter, most physicians give them, and they are essential in cholangitis. Antibiotics, however, are not an alternative to appropriate biliary drainage. If used, antibiotic coverage should include drugs directed against Gramnegative rods and enterococci as well as anaerobes. Piperacillin-tazobactam, ampicillin-sulbactam, ticarcillin-clavulanate, and the carbapenems are all rational initial choices. (A third- or fourth-generation cephalosporin plus metronidazole or clindamycin or ampicillin, gentamicin, and clindamycin are acceptable alternative combinations.)

Most patients with uncomplicated cholecystitis should undergo cholecystectomy after stabilization and before discharge from the hospital. Surgical (laparoscopic or open) cholecystectomy is the procedure of choice. Mortality rates for cholecystectomy in this setting are less than 1% but may rise in elderly patients. Urgent surgery is indicated for patients with common bile duct obstruction with or without cholangitis, emphysematous cholecystitis, or perforation of the gallbladder and for those who deteriorate while receiving antibiotic and fluid support. Early surgical intervention reduces the risk of suppurative complications, duration of hospital stay, and mortality. Severity of illness in biliary tract obstruction should not preclude surgery because drainage offers the best chance for recovery. In the critically ill patient, it is generally best to do the simplest effective procedure. Less invasive options include percutaneous catheter drainage, a useful technique in the high-risk ICU patient or in the terminally ill that can be performed by an interventional radiologist. Unfortunately, bile peritonitis, a
potentially lethal problem, may complicate this procedure. ERCP is another option that may be performed without general anesthesia. ERCP is most helpful for stones impacted in the ampullary region, but cannulation can be difficult because of ampullary edema and obstruction.

**Small Bowel Obstruction**

The triad of nausea, vomiting, and acute abdominal pain should suggest small bowel obstruction (SBO). SBO can be classified as (1) simple, (2) strangulated (in which vascular compromise is the predominant manifestation), or (3) closed loop (in which vascular compromise and complete bowel obstruction rapidly increase intraluminal pressure). Seventy-five percent of cases are due to postoperative adhesions, whereas, incarcerated hernias and malignancy comprise the majority of the remainder. Inflammatory bowel disease, intussusception, and gallstones account for a small minority of cases.

On examination, blood in the stool signifies compromised bowel wall integrity. Incarcerated hernias or abdominal scars are suggestive physical findings. Bowel sounds are usually rushing and high pitched early in SBO but later become hypoactive. Flat abdominal radiographs demonstrate dilated small bowel loops (>3 cm), whereas those taken with the patient in the upright position demonstrate small bowel dilation and multiple air-fluid levels, sometimes with distal evacuation of the colon and rectum. CT scan of the abdomen is now the diagnostic test of choice.

Treatment of SBO is usually less urgent than treatment of colonic obstruction. However, strangulated bowel with perforation, a potentially disastrous problem, is often misdiagnosed as simple SBO. Unfortunately, there is no clinical way to distinguish between simple SBO and strangulated bowel. Good candidates for conservative management with nasogastric suction include patients who are hemodynamically stable, those with a partial SBO, those with recurrent obstruction following radiation therapy, and those with SBO occurring within 30 days of abdominal surgery. Failure to symptomatically improve with gastric suction suggests operative intervention is required.

Over 80% of patients with SBO will recover without operation. A clinical challenge is identifying the patient who requires operative intervention prior to the onset of complications. Signs and symptoms of compromised perfusion of the small bowel, including continuous abdominal pain, fever, leukocytosis, tachycardia, signs of peritoneal irritation, elevated amylase level, and metabolic acidosis, are not reliable for diagnosing intestinal ischemia or complete bowel obstruction. Where CT scan is utilized to evaluate patients with SBO, factors strongly associated with the need for urgent operation are bowel wall thickening and gas in the bowel wall. Many centers now administer water-soluble contrast agents and follow patients with serial plain abdominal radiographs to confirm passage of contrast to the colon. In general, where water-soluble contrast passes to the colon occurs within the initial hours after its administration through a nasogastric tube, the patient will not require operation, and diet and activity can be rapidly advanced. Complications associated with water-soluble contrast administration, such as aspiration and anaphylaxis, are serious but uncommon.

**Colonic Obstruction**

Colonic obstruction, a disease predominately of the elderly, presents with acute abdominal pain, prodromal constipation or obstipation (50%), and nausea and vomiting (50%). The most common causes of obstruction include colon cancer, diverticular disease, and volvulus. When volvulus occurs, the sigmoid is the most commonly involved site (75%), followed by the cecum. Fecal impaction may imitate this picture. About 20% of patients with colon cancer will have both perforation and obstruction, demonstrating free air on abdominal radiographs. The plain radiograph may be quite helpful in colonic obstruction. When obstruction is mechanical, a “cutoff” sign is often seen at the level of obstruction with air in the proximal colon and small bowel and a gasless distal colon. Plain radiographs are diagnostic of volvulus in more than 50% of patients. When radiographs show
an acute increase of cecal diameter to more than 10 cm, perforation of the colon may be imminent. The CT scan is a very valuable diagnostic tool to identify not only the location but also the cause of obstruction preoperatively. CT has almost entirely supplanted previous diagnostic techniques (e.g., barium enema and colonoscopy) because of its low risk and high yield.

“Pseudo-obstruction” (Ogilvie syndrome) may occur in which signs and symptoms of bowel obstruction are present without a mechanical cause. Although uncommon, pseudo-obstruction has been associated with spinal disease, trauma, heart failure, electrolyte imbalances (magnesium or potassium), narcotics, anticholinergic drugs, myxedema, or ganglionic blockers, but its mechanism is unknown. Nausea, vomiting, abdominal pain, and, paradoxically, diarrhea are common symptoms. Bowel sounds are present in almost all cases, and the abdomen is usually distended and tympanitic. The colonic dilation of pseudo-obstruction usually occurs in the right and transverse colon but may extend to the rectum. After excluding mechanical obstruction and toxic megacolon, treatment consists of withholding food, correcting underlying conditions, and carefully observing the patient for complications. Decompression by colonoscopy or percutaneous cecostomy is rarely necessary, and there is little agreement about where the risk-benefit ratio lies for these interventions. There is general consensus that operative interventions should be the last resort. Similarly, although cholinergic agents (i.e., neostigmine), erythromycin, and other prokinetic compounds have been tried, there is no consensus with regard to success or risk. A newer compound methylnaltrexone has shown promise for colonic pseudo-obstruction associated with opioid use. Side effects are those to be expected from a compound that promotes bowel motility (i.e., nausea, abdominal pain, and flatulence).

Toxic megacolon is an inflammatory-ischemic condition most often seen as a complication of chronic inflammatory bowel disease (e.g., Crohn disease) or acute infectious colitis (e.g., *C. difficile*). Interestingly, several types of infectious colitis (e.g., *Salmonella*, *Shigella*, *Campylobacter*, *Entamoeba*), even when severe, are unlikely to cause toxic megacolon. Cytomegalovirus is a potential cause in the HIV-infected patient. The precise mechanism of toxic megacolon is not known but probably involves extension of the underlying infectious or inflammatory colitis through colonic mucosa into the smooth muscle layer. When this invasion occurs, peristalsis stops and the colon dilates. Colonic dilation may lead to local ischemia by compressing the vascular supply. Because the mucosa is injured, hematochezia is common. The diagnosis of toxic megacolon is a clinical one made by the combination of nonobstructive colonic distention in a patient with appropriate risk factors who appears “toxic.” The right and transverse portions of the colon are most frequently involved, with colonic dimensions occasionally reaching 15 cm. Imaging studies confirm the diagnosis and facilitate anticipation of complications. Colonoscopy, although usually diagnostic, can lead to perforation. In a patient with an acute abdomen, immediate laparotomy with colectomy is indicated. For patients appearing less toxic, treatment of the underlying condition (e.g., oral vancomycin for *C. difficile* colitis or corticosteroids for inflammatory bowel disease) coupled with careful observation is the best path. When remote organs fail, colectomy should be seriously considered.

**Diverticulitis**

Diverticulitis, the result of an inflamed pseudodiverticulum, accounts for up to 10% of all abdominal pain in the elderly. Even though diverticulitis has been referred to as “left-sided appendicitis,” the pain has no typical pattern. Nausea, fever, and constipation are common, but vomiting is quite unusual. Physical examination may demonstrate a palpable mass in the lower abdomen or pelvis. Although often guaiac positive, the stool is rarely bloody. Colonoscopy is often necessary to rule out neoplasm because the extrinsic compression of the bowel caused by diverticulitis mimics colon carcinoma. Abdominal CT is useful to demonstrate bowel wall inflammation, pericolic edema, and fistula or abscess formation. Resuscitation and antibiotic therapy is successful in 80% to 90% of cases. Withholding food and providing mild analgesia, nasogastric suction, and IV fluids are standard.
Broad-spectrum antibiotics (e.g., to treat Enterobacteriaceae and anaerobes) should be administered. The majority of episodes of diverticulitis can be managed without operation. Indications for operation in diverticulitis include perforation, obstruction, abscess formation, fistula tract formation, malignancy, and failure to respond to several days of conservative management.

**Retroperitoneal Hemorrhage**

Retroperitoneal hemorrhage rarely occurs spontaneously. Retroperitoneal hemorrhage usually results from trauma, surgery, invasive procedures (e.g., vena caval filter placement), or anticoagulation. Most patients present with nonspecific flank or abdominal pain—a minority have shock or an acute abdomen. A common vexing problem from retroperitoneal bleeding is the development of severe ileus. Although typically the hematocrit does not rapidly decline, the retroperitoneum is one of the few anatomic compartments capable of containing a massive hemorrhage without evidence of external blood loss. US is not routinely helpful. CT scan is the diagnostic procedure of choice to clearly demonstrate the extent of the bleeding, although it may not identify a specific site unless a contrast blush is observed. Lacking evidence of obvious extravasation of contrast (i.e., vena cava, renal or splenic artery, or other named vessels), treatment is supportive, with reversal of any existing coagulation disorder and support of the hematocrit and blood pressure. Even though significant blood loss can occur, nonoperative treatment is frequently effective, and blind surgical exploration rarely identifies a discrete bleeding source amenable to repair. Interventional radiology techniques can follow up on contrast blush changes detected on CT scan. Patients with adrenal hemorrhage as the result of infection or anticoagulation can have an identical clinical presentation with nonspecific flank pain. The diagnosis is confirmed by a CT that demonstrates adrenal hemorrhage and by blood testing that reveals primary adrenal insufficiency (see Chapter 32).

**Perforated Viscus**

Free air detected under the diaphragm can be the result of a supradiaphragmatic or subdiaphragmatic process. (Recent abdominal surgery and percutaneous gastrostomy (PEG) tube placement are common benign causes.) Pulmonary barotrauma can result in eventual dissection of air into the peritoneal cavity, making a certain diagnosis of a perforated viscus difficult. When free air is detected below the diaphragm as a result of perforation of an intra-abdominal organ, the proximal GI tract is the most likely source. Because perforation of the stomach or duodenum is much more common than colonic perforation, consideration of a source in the upper GI tract should precede laparotomy for presumed colonic perforation. Although a small amount of free intraperitoneal air is normal following PEG tube placement, if free abdominal fluid or large collections of peritoneal air are seen, especially days after placement, tube malpositioning should be suspected. Likewise, any patient with free abdominal air and/or fluid following therapeutic PEG tube manipulation or self-extraction should prompt consideration of a communication between bowel and peritoneum. Residual free intraperitoneal air is also common in the early days after laparotomy or a laparoscopic procedure.

**Ulcer-Induced Perforation**

The perforated gastric or posterior duodenal ulcer is often misdiagnosed as pancreatitis because of similar symptomatology (midabdominal pain radiating to the back, nausea, vomiting, and elevated serum amylase). By contrast, anterior ulcer perforations produce a chemical peritonitis with diffuse acute abdominal pain and ileus. Perforation more commonly complicates duodenal (5% to 10%) than gastric ulcers (<1%). Patients with perforated ulcers usually appear very ill with diffuse acute abdominal pain, tenderness, and decreased bowel sounds. If the process is not recognized, frank peritonitis and shock ensue. A minority of such patients have the abrupt onset of acute abdominal pain or a rigid abdomen. About 80% of all ulcer perforations release free air into the peritoneal cavity. To demonstrate free abdominal gas on plain radiograph, it may be necessary to position the patient upright or in the left lateral decubitus posture for 5 to 10 minutes before film exposure. (Abdominal CT
is highly sensitive for perforation.) If free air is not seen on plain film and CT is not feasible, a perforation may be confirmed by demonstrating extravasation of water-soluble contrast (e.g., Gastrografin, not barium) into the peritoneum. Surgical intervention is indicated in ulcer disease for uncontained perforation, bleeding which cannot be controlled by endoscopic or interventional radiology techniques, and gastric outlet obstruction. Intractable pain is an uncommon indication for surgery. Occasionally, limited gastric resection may be indicated along with a drainage procedure to assure adequate gastric emptying. Most patients who go to the operating room, however, have biopsies performed of the ulcer and closure with a patch of omentum. In unstable patients, however, the ulcer should be oversewn and the operation quickly terminated. Whenever possible, gastric ulcers should be resected or multiple biopsies obtained because of the higher potential for carcinoma.

**Colonic Perforation**

Perforation of the colon is frequently associated with colonic obstruction because of malignancy or diverticular disease. Diverticular perforation is frequently responsible for free intraperitoneal gas in the elderly, but many (possibly most) perforated diverticuli do not liberate intraperitoneal gas. Colonic perforation requires fluid resuscitation, antibiotic therapy, and surgical intervention for patients who do not improve with antibiotics, drainage, and fluid resuscitation. Operations often include at least partial colonic resection and colostomy.

**UNUSUAL CAUSES OF ACUTE ABDOMINAL PAIN**

Carcinoma is found in 5% to 10% of elderly patients with acute abdominal pain. Although no one knows the cause, patients with diabetic ketoacidosis sometimes present with acute abdominal pain. (Diabetic ketoacidosis should be excluded in all patients before laparotomy.) Sickle cell disease may produce abdominal pain by infarcting the bowel or spleen. Inferior myocardial infarction and pneumonia in the basilar segments of the lung may both present with abdominal discomfort. In these patients, nausea and vomiting are also common, mimicking acute cholecystitis. In such cases, a detailed history, careful examination, and chest radiography are diagnostic. Typhlitis, bacterial invasion of the bowel wall in immunosuppressed patients, may be confused with ischemic colitis, diverticulitis, or appendicitis. Several forms of chemotherapy may produce nausea, vomiting, and GI bleeding (particularly cytosine arabinoside). Up to one fourth of all leukemic patients have neoplastic infiltration of the bowel wall that may cause perforation either in the natural history of the disease or shortly after the initiation of chemotherapy.

**SUGGESTED READINGS**


Chapter 37
Gastrointestinal Bleeding

• Key Points

1. Prophylactic treatment methods include acid suppression or neutralization, maintenance of good splanchnic perfusion, and provision of enteral feeding as early as tolerated.

2. Upper gastrointestinal bleeds are usually readily distinguished from lower tract bleeds by simple history and physical examination. Vomiting blood is a highly reliable sign of upper gastrointestinal bleeding, whereas hematochezia may result from an upper or lower source. Melena suggests but does not confirm an upper tract bleeding source.

3. With the notable exceptions of varices and ulcers containing visible vessels or overlying clots, most gastrointestinal bleeding usually ceases spontaneously.

4. Esophagogastroduodenoscopy provides a rapid, safe, and usually precise method to diagnose the source of upper gastrointestinal bleeding, offers several therapeutic options (injection therapy, thermal coagulation, variceal banding), and provides useful prognostic information.

5. Significant lower gastrointestinal bleeding is less common than bleeding from an upper source. Once bleeding slows and the bowel can be evacuated, colonoscopy provides a diagnosis in most cases. With briskly bleeding lower gastrointestinal lesions, angiography or nuclear scans offer alternative diagnostic options.

The anatomic point of division between upper and lower tract bleeding is regarded as the ligament of Treitz. Common upper gastrointestinal (UGI) sources of hemorrhage include ulceration, stress-related gastric mucosal injury, and varices of the esophagus and stomach. Common causes of lower gastrointestinal (LGI) bleeding include diverticulosis and arteriovenous malformation. Endoscopic evidence of bleeding can be identified in 75% to 100% of intensive care unit (ICU) patients. Clinically significant bleeding occurs in 1% to 5% of ICU patients. Bleeding becomes overt in 5% to 25% of these cases via associated coffee-ground aspirate and/or guaiac-positive stool. Patients with hemodynamic instability and a decrease in hemoglobin exceeding 2 g/dL may require transfusion. Overt bleeding often complicates serious underlying disease, extends ICU length of stay, and contributes to mortality risk, especially among patients who bleed later in their ICU stay.

PREVENTION

In decades past, the development of UGI bleeding from diffuse “stress ulceration” complicated the stay of up to 30% of critically ill patients. Fortunately, the incidence of significant UGI bleeding developing in the ICU has declined dramatically. Although this is partly the result of the widespread use of histamine (H2) blockers, proton pump inhibitors (PPIs), and other gastroprotective agents, many other practices have also contributed. For example, it is much more common to initiate mucosa-protective enteral nutrition earlier and in preference to total parenteral nutrition (TPN). Use of ulcerogenic medications including corticosteroids, slow-release potassium tablets, and oral nonsteroidal anti-inflammatory agents is also less common. Because shock is a potent risk factor for mucosal ulceration and mesenteric ischemia, it is also likely that more aggressive resuscitation practices are partly responsible for the reduced risk of bleeding. Finally, improved sedation, ventilation, and weaning protocols have shortened the time on mechanical ventilation,
EVALUATION OF THE BLEEDING PATIENT

First Steps

Indications
Not all ICU patients require pharmacologic “ulcer prophylaxis”; however, such prevention is indicated for those undergoing prolonged (>48 hours) mechanical ventilation, for patients with coagulation disorders (e.g., thrombocytopenia, consumptive, hereditary, or anticoagulation-related), and for patients with renal failure. Other reasonable candidates include patients with burns, trauma, head or spinal injury, and those receiving corticosteroids. As the number of risk factors for bleeding mounts, so should the incentive to prescribe prophylaxis. For patients receiving enteral nutrition, prophylaxis may add cost and potential for infective hazard, without potential benefit, especially for those not ventilated.

Medication Options
If mucosal protection or pharmacologic gastric acid buffering is deemed necessary, H₂ blockers and PPIs (proton pump inhibitors) are available to accomplish the task. No convincing data suggest the superiority of one class of agent over another or the superiority of any specific drug within a class. Hence, drug selection should be based on side effect profile, cost, and convenience.

Because the efficacies of continuous intravenous (IV) infusions, intermittent injections, and oral dosing of available H₂ blockers appear equivalent, it is reasonable to use the least expensive oral agent when possible. Significant side effects of H₂ blockers are rare but include altered drug metabolism and confusion (most frequently reported with cimetidine). Although often discussed, there is little convincing evidence that H₂ blockers promote thrombocytopenia.

By inhibiting the final step in acid secretion, PPIs given once or twice daily effectively raise gastric pH to a greater degree and for longer periods than H₂ blockers. Despite this observation, there are no credible data to suggest that PPIs given either IV or enterally are superior to H₂ blockers for the primary prevention of UGI bleeding. Some PPIs (e.g., lansoprazole, omeprazole) are supplied as capsules containing enteric-coated granules, which must be suspended in a pH-buffering vehicle if administered by tube. These preparations may clog small-bore feeding catheters. As a group, PPIs are very safe, but their use increases the absorption of digoxin, calcium channel blockers, benzodiazepines, and opiates. The clinical importance of rebound acid hypersecretion is uncertain but may occur after discontinuation of PPIs.

Risks
Although debated, gastric acid suppression, regardless of how it is achieved, is probably associated with a small increase in the risks of nosocomial pneumonia and Clostridium difficile colitis. The mechanisms relate to gastric overgrowth of pathogenic microorganisms and aspiration. Not only does gastric pH play a role in aspiration pneumonia risk, but stomach volume and patient position do as well—elevation of the head of the bed will reduce this hazard. For most patients, the benefit to risk balance favors bleeding prophylaxis. When prophylaxis is used, effective measures to lower the risk of pneumonia are to elevate the head of the bed to at least 30 degrees, to avoid bolus enteral feedings, and to provide consistent oral hygiene. Doing so reduces the reflux of gastric contents and the potential for aspiration and lowers the burden of pathogenic organisms that may be aspirated.
In patients with conspicuous gastrointestinal (GI) bleeding, attention should first be devoted to ensuring a stable airway, providing adequate ventilation, and establishing adequate intravenous access. Developing an appropriate and efficient diagnostic and therapeutic plan requires distinguishing upper from lower bleeding using historical and demographic information as well as the physical examination. UGI bleeding is more likely among younger patients and men. A history of repeated retching, nonsteroidal anti-inflammatory drug (NSAID) use, heavy alcohol ingestion, prior peptic ulceration, or liver disease (especially with varices) favors an UGI bleeding source. By contrast, lower GI (LGI) bleeding is more likely among older patients, women, and patients with a history of diverticular or vascular occlusive disease. GI bleeding during systemic anticoagulation does not preferentially occur from an upper or lower source.

**Examination**

Bruising and petechiae may be clues to an underlying coagulopathy, and cutaneous or mucous membrane arteriovenous malformations may signal the presence of hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). The stigmata of cirrhosis and portal hypertension (e.g., jaundice, ascites, spider angiomata, caput medusa, palmar erythema, gynecomastia, ecchymoses) make a diagnosis of UGI bleeding much more likely.

The predominant portal of blood loss (oral or rectal) provides a valuable clue to bleeding site. Hematemesis is rarely the result of LGI bleeding and essentially never results from a source beyond the proximal jejunum. By contrast, hematochezia can result from brisk upper or lower LGI bleeding, but in the absence of shock is almost always due to an LGI source. As little as 15 mL of blood in the UGI tract may produce guaiac-positive stools, but melena (black, tarry stools formed by the digestion of blood by acid and bacteria) requires loss of more than 100 mL of blood over a relatively brief period. Because blood in the gut speeds transit time, melena seldom results from LGI bleeding unless it originates from a slow bleed in the ascending colon. More commonly, significant bleeding from the right colon produces maroon-colored stools, whereas bleeding from the left colon results in hematochezia. A mixture of formed stool with red blood is highly suggestive of a distal colonic (sigmoid colon or rectal) source.

An UGI bleed is less likely if the aspirate from a gastric tube does not reveal fresh blood or at least “coffee-ground” material, although as many as 15% of patients with UGI bleeding have clear aspirates. These “false” aspirates usually occur when a competent pylorus prevents reflux of blood originating in the duodenum into the stomach. Testing gastric contents for occult blood is not warranted because it commonly produces false-positive results.

**Assessing Bleeding Severity**

Unless very abrupt, blood losses of < 1 L in the absence of other disease may produce few physiological changes, as pulse, respiratory rate, blood pressure, mental status, and urine output remain nearly normal. With acute losses of 1 to 1.5 L, tachycardia, tachypnea, oliguria, and orthostatic blood pressure changes are detectable. Tachypnea can be an appropriate compensatory response to hemorrhage and metabolic acidosis, a consequence of aspirating vomited blood, or simply a manifestation of anxiety. Moderate shock following hemorrhage of 1.5 to 2 L raises pulse and respiratory rate further, causes confusion, slows capillary refill, and further diminishes urine output. When severe shock occurs, typically with blood losses greater than 2 L, hypotension may be profound, tachycardia may be marked, and enormous ventilatory demands may cause respiratory distress; urine output and mental status are virtually never normal. During acute hemorrhage, it is important to not be misled by hemoglobin (Hgb) measurements. In severe acute blood loss, the Hgb concentration can remain nearly normal despite massive losses until crystalloid replacement is begun. By
contrast, a very low Hgb concentration in a patient with nearly normal vital signs almost certainly means blood loss has occurred over weeks or even months. Hence, shock with visible loss of large volumes of blood should prompt aggressive transfusion, whereas severe anemia without visible evidence of blood or shock can be approached more slowly.

**Initial Treatment**

As stabilization is accomplished, appropriate consultants (e.g., gastroenterology, interventional radiology, surgery) should be notified. For patients with shock, massive hematemesis, depressed consciousness, or impending respiratory failure, it usually makes sense to perform urgent endotracheal intubation before overwhelming aspiration or respiratory arrest occurs. In addition, upper endoscopic evaluation is often not possible without deep sedation and airway control. Caution is advised, however; frequently, massive hematemesis obscures the airway. Effective suction and expert backup are essential. When time permits, evacuation of the stomach with a gastric tube may reduce regurgitation risk. Gown, gloves, and face-shield protection for the proceduralist is prudent.

Regardless of bleeding source, at least two largebore (14- to 16-gauge) peripheral IV catheters or a large central venous catheter (CVC) should be inserted to allow rapid fluid and blood administration. A CVC is always necessary and may not be the best choice for fluid infusion, but the central venous pressure (CVP) measurements it yields can provide a useful (if imperfect) guide to fluid replacement. (A triple-lumen catheter may actually slow fluid administration because its three smaller lumens and increased length cannot achieve the same infusion rates as shorter, larger-bore peripheral IVs.) By contrast, a centrally placed 7.5- or 8.5-F conduit can deliver prodigious amounts of fluid and blood, especially if used with a pressurized infuser.

At the time IV access is obtained, samples should be drawn for Hgb, electrolytes, creatinine, liver function tests, prothrombin time (PT), platelet count, and blood typing and cross-matching. Arterial blood gases may be useful to evaluate adequacy of ventilation and severity of metabolic acidosis. The basic principles of supporting the circulation and transfusion are presented in Chapters 3 and 14, respectively; however, a few points deserve emphasis. First, the fundamental problem in severe GI bleeding is intravascular volume depletion. Therefore, the best initial therapeutic step is not vasopressor infusion but isotonic crystalloid replacement, followed by blood when necessary. Colloid offers no demonstrated advantage over isotonic crystalloid resuscitation, despite the fact that a smaller volume of the former is required to produce equivalent volume expansion. Colloids are not always immediately available and are more expensive than crystalloids for equal effect. Although fresh whole blood offers marginally more effective oxygen delivery than older packed red blood cells, it is rarely available. As a consequence, blood replacement is usually accomplished using specific component therapy with serial assessments of Hgb, platelet count, and PT. For exsanguinating patients, universal donor (O negative) blood may be necessary, but if there are even a few minutes to spare, the safer alternative is type-specific red blood cells. Thrombocytopenia or soluble clotting factor deficiencies should be corrected rapidly to promote hemostasis. Prevention and reversal of hypothermia and metabolic acidosis are additional methods of optimizing coagulation. Reasonable transfusion goals are ≥50,000/mm$^3$ functioning platelets, a PT less than 1.5 times control, and a Hgb of 8 to 10 g/dL. Although it is clear that lower transfusion thresholds are safe for the nonbleeding patient, it is prudent to maintain a buffer against exsanguination during ongoing hemorrhage. Even higher Hgb values may be appropriate in patients with critical oxygen supply problems such as recent myocardial ischemia or stroke.

Retrospective studies of military casualties and similar work in civilian trauma centers show improved
survival with transfusion of one unit of fresh frozen plasma and one platelet unit for each unit of red blood cells administered. These studies have been criticized for methodologic flaws including survival bias (patients who did not survive were not transfused with fresh frozen plasma and platelets in comparable amounts). Increased use of plasma is not without risk as the incidence of transfusion-related acute lung injury is increased, as may be the risk of ARDS. If available, another alternative to plasma is administration of specific factor concentrates based on ongoing laboratory testing.

In patients with major bleeding, more fibrinogen is required than any other hemostatic protein. In actively bleeding patients, it is depleted and rendered less effective by fibrinolysis, hemodilution, and consumption. Guidelines for the management of traumatic bleeding now indicate that the trigger level for supplementing fibrinogen should be 1.5 to 2.0 g/L rather than 1.0 g/L. Tranexamic acid, an inhibitor of fibrinolysis, has been demonstrated to reduce the need for blood transfusion in surgery and is now strongly recommended for the injured patient with bleeding. This experience may be applicable to the patient with significant gastrointestinal bleeding, as well. For most patients with UGI bleeding, gentle placement of a nasogastric (NG) or orogastric (OG) tube is safe and useful for monitoring the rate of bleeding. Although controversial, probable exceptions should include patients with esophageal varices or Mallory-Weiss tears in whom OG tube placement theoretically could aggravate bleeding. Combining clinical data with gastric aspirate results also has prognostic value. Clear or coffee-ground returns portend a good prognosis when the patient presents initially with melena. When red blood is aspirated from the stomach of a patient with melena, the prognosis is worse—but not as bad as when red blood is recovered from the stomach during hematochezia. Patients with liver failure may benefit from purging intestinal blood that can precipitate hepatic encephalopathy, but blood is an excellent laxative, usually making cathartics unnecessary. Gastric lavage does not decrease the rate of UGI bleeding, even when the solution is cooled or fortified with a vasoconstrictor.

UPPER GASTROINTESTINAL (UGI) BLEEDING

Sources

A relatively small number of conditions are responsible for most cases of UGI bleeding (Table 37-1). Peptic ulcer disease (gastric and duodenal ulcer) leads the list, followed by gastric and esophageal erosive disease, Mallory-Weiss tears, and variceal bleeding. Making a definitive diagnosis of an UGI bleeding source usually is straightforward during endoscopy (Fig. 37-1). Fortunately, regardless of cause, UGI bleeding stops spontaneously in 70% to 80% patients. A combination of clinical factors (i.e., older age, shock at presentation, coagulopathy, or renal, hepatic, or heart failure) and specific endoscopic findings (Table 37-2) predict those most likely to have recurrent bleeding.

<table>
<thead>
<tr>
<th>Source</th>
<th>Approximate Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer disease</td>
<td>50%</td>
</tr>
<tr>
<td>Erosive gastritis-esophageal</td>
<td>25%</td>
</tr>
</tbody>
</table>
### Diagnostic Tests

Plain abdominal radiographs are rarely useful in making a relevant diagnosis unless they demonstrate free air (indicating perforation of a viscus) or “thumbprinting” of the large bowel (suggesting ischemic colitis). Likewise, the long-used “UGI series” is seldom diagnostic and swallowed barium compromises subsequent tests, including endoscopy, CT scanning, and angiography. Barium studies also require transport of potentially unstable patients to the radiography suite.

![Diagram of suggested diagnostic evaluation](image)

**FIGURE 37-1.** Suggested diagnostic evaluation of suspected upper GI bleeding. If upper GI bleeding is
believed to be likely after obtaining a history and performing a physical examination, esophagogastroduodenoscopy (EGD) is usually performed. If EGD is diagnostic, therapy directed at the specific lesion should be instituted. If the EGD is normal, the small bowel or LGI tract should be considered as a bleeding source. When the EGD is abnormal but nondiagnostic, consideration should be given to mesenteric angiography.

<table>
<thead>
<tr>
<th>Endoscopic Finding</th>
<th>Risk of Rebleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visible bleeding vessel</td>
<td>Near 100%</td>
</tr>
<tr>
<td>Active oozing</td>
<td>30%-80%</td>
</tr>
<tr>
<td>Nonbleeding vessel</td>
<td>50%</td>
</tr>
<tr>
<td>Esophageal varices</td>
<td>50%</td>
</tr>
<tr>
<td>Red or black “spot”</td>
<td>5%-10%</td>
</tr>
<tr>
<td>Clean ulcer base</td>
<td>1%</td>
</tr>
</tbody>
</table>

Esophagogastroduodenoscopy (EGD) is a high-yield procedure to (1) definitively demonstrate the bleeding site, (2) predict the likelihood for rebleeding, (3) permit control of some lesions, and (4) reduce resource utilization (e.g., transfusions, operating room time if surgery is required, and hospital length of stay). However, EGD has several limitations: sedation may compromise ventilation in tenuous patients, and an optimal examination requires a stomach empty of food and blood. (A single 250-mg dose of IV erythromycin given 30 minutes before endoscopy can increase gastric emptying and improve visualization.)

The best time to perform EGD is debated but is probably as soon as the airway is secured, oxygenation is adequate, and a degree of hemodynamic stability is achieved. Based on the combination of clinical and endoscopic features, it is safe to provide care outside the ICU and even discharge patients with lesions at low risk to rebleed (i.e., gastritis, clean-based ulcers, or flat pigmented spots). By contrast, patients with bleeding varices and those with ulcers containing visible vessels or obscured by overlying clot are at high risk for recurring hemorrhage.

Endoscopic injection therapy using epinephrine is a safe and effective method to gain initial control and prevent rebleeding in high-risk nonvariceal lesions. Similarly, thermal therapy (i.e., bipolar electrocoagulation, probe coagulation) has been used alone and in combination with injection therapy to arrest and deter recurrent hemorrhage. Surprisingly, removing a clot overlying an ulcer and then using injection and/or thermal therapy reduces the risk of rebleeding compared to not disturbing the clot. (Perhaps because without vasoconstriction and coagulation of the underlying vessels, hemorrhage is more likely to recur when the clot is spontaneously dislodged or dissolved.) Among the 15% to 20% of patients who rebleed, such events typically occur within 48 hours of initial EGD. The particular technique used to halt bleeding is determined largely by operator preference.
because all endoscopic methods have comparable effectiveness and safety. Uncommon risks of these procedures include worsening of bleeding and perforation. Use of a PPI after endoscopic therapy for high-risk ulcer lesions reduces rebleeding even further, but benefits do not extend to nonulcer bleeding sources, and it is not known if H₂ blockers offer similar benefit.

If a technically satisfactory EGD fails to reveal a bleeding source, three possibilities exist: the upper bleeding source is beyond the reach of the endoscope (e.g., small bowel); the bleeding has stopped spontaneously; or the source is in the LGI tract. When an upper bleeding source is elusive, evaluation of the lower tract is indicated; however, it is not prudent to hastily dismiss the possibility of an UGI source, even after “negative” EGD. More often than expected, bleeding from an esophageal or gastric varix goes unrecognized as volume depletion collapses the normally distended veins and spontaneously arrests hemorrhage. Frequently, it is not until circulating volume is restored until patients again begin to bleed. If bleeding recurs, endoscopy should be repeated. When vigorous bleeding prevents identifying the bleeding site, angiography is the next most useful course of action. (It is also the preferred procedure to diagnose small bowel hemorrhage.) During angiography, bleeding may be stopped by infusing vasoconstrictors or by embolizing the bleeding vessel.

Specific Causes of UGI Bleeding

Peptic Ulcer Disease

Nearly one half of all cases of UGI bleeding in many ICUs are due to peptic ulceration (Fig. 37-2). Common conditions predisposing to peptic ulcer bleeding are nonsteroidal anti-inflammatory agent use and Helicobacter pylori infection. Hyperacidity is less common. Although most ambulatory patients with ulcers relate a history of epigastric pain (particularly nocturnal) relieved by food, H₂ blockers, PPIs, or antacids, pain is rare among ICU patients. EGD is the diagnostic procedure of choice because it is safe, rapidly performed, and may facilitate control of bleeding with thermal coagulation or injection therapy. Even when bleeding cannot be controlled, information gained from EGD assists in planning definitive therapy.

The overall risk of recurrent bleeding from ulcer disease is 20% to 30%, but certain EGD findings portend higher risk and indicate that aggressive or earlier intervention is indicated (see Table 37-2). Visualization of persistent active bleeding from a visible vessel mandates endoscopic, angiographic, or surgical intervention because of the extremely high (approaching 90%) chance of continued or recurrent hemorrhage. When a nonbleeding vessel is seen in an ulcer crater, the risk of rebleeding approaches 50%. An adherent clot overlying an ulcer predicts rebleeding in as many as a quarter of patients, again suggesting that endoscopic or surgical intervention probably is indicated. A lesion oozing blood without a visible vessel has only about a 10% risk of refractory bleeding, and flat pigmented spots or smooth ulcer bases carry an even lower (1% to 10%) risk. Consequently, they usually are treated medically. Ulcer location also provides information about the likelihood of rebleeding. Ulcers high on the lesser gastric curvature (over the left gastric artery) and on the posterior-inferior wall of the duodenum (overlying the gastroduodenal artery) are the most ominous. Fortunately, most ulcers stop bleeding spontaneously with supportive care and control of gastric pH. Persistent severe hemorrhage should prompt consideration of surgery or angiographic occlusion. Although the relationship of H. pylori infection to ulcer disease and need to treat is well accepted, no benefit of antimicrobial treatment has been demonstrated regarding control of active hemorrhage.
Gastritis
Erosive gastritis and/or esophagitis is the second most frequent cause of GI bleeding in the ICU and is particularly common in critically ill patients with respiratory failure, sepsis, hypotension, or burns. Although "superficial," stress ulceration may result in severe bleeding, particularly in patients with underlying coagulopathy or receiving anticoagulation. These erosions result from the combined actions of acid, ulcerogenic drugs, NG tube irritation, and ischemia on mucosal surfaces and typically develop 5 to 7 days after admission to the ICU. H$_2$ blockers and PPIs reduce the incidence of gastritis, but the best preventative measures are avoidance of hypotension and hypoxia and early provision of enteral nutrition.

Early bleeding (less than hours) tends to arise in proximal ulceration of the gastric fundus. Later bleeding tends to emanate from a more distal location, usually from erosive ulcers in the duodenal region. Better resuscitation, enteral nutrition, and drug prophylaxis with H$_2$ receptor antagonists or PPIs reduce the incidence of bleeding among “at risk” patients to about 4%. High-risk patient groups include solid organ transplant, patients with traumatic brain injury, and individuals with major burns.

Mallory-Weiss Tears
Forceful retching may disrupt the mucosa of the gastroesophageal junction, resulting in a Mallory-Weiss tear. These longitudinal mucosal lacerations account for 5% to 15% of all UGI bleeding and are much more common in men than in women. Precipitating or contributing factors include (1) alcohol use, (2) intractable vomiting, and (3) esophageal food impaction. Rarely, coughing, seizures, heavy lifting, pregnancy, and upper endoscopy have been associated with such lesions. Interestingly, no precipitating event is evident in approximately 20% of cases. Even though these lesions commonly lead to massive hemorrhage, bleeding almost always stops spontaneously. The diagnosis is suggested by a history of forceful, painless hematemesis and is confirmed by an EGD demonstrating linear tears on the gastric side of the gastroesophageal junction. Supportive treatment includes antiemetics, raising gastric pH, and expectant observation. In the unusual instance in which bleeding does not
promptly abate, EGD with thermal coagulation or therapeutic injection can halt bleeding. Surgery to control hemorrhage rarely is necessary unless the tear involves preexisting esophageal varices.


Portal Hypertension and Variceal Bleeding

Varices are fragile, bulbous venous channels that shunt portal blood to the systemic circuit driven by portal hypertension (Fig. 37-3). These native shunts usually are the result of cirrhosis induced by ethanol and/or viral hepatitis, but portal hypertension has many potential causes, spanning the anatomic spectrum from the portal to hepatic vein (Table 37-3). The largest of these collateral channels tend to form at the gastroesophageal junction; however, hemorrhoidal and retroperitoneal veins also dilate and bleed. As many as 40% of all patients with advanced cirrhosis eventually develop variceal hemorrhage characterized by abrupt, painless, massive UGI bleeding. The risk of bleeding correlates roughly with the size of the varices, the severity of the underlying liver disease, and the magnitude of the hepatic venous pressure gradient. (Bleeding is uncommon when the gradient is <12 mm Hg.) Variceal hemorrhage often is difficult to treat because of accompanying coagulation abnormalities. Soluble clotting factor deficiencies commonly result from malnutrition or impaired hepatic synthetic function. Furthermore, ethanol suppression of the bone marrow and portal hypertension-induced hypersplenism often cause thrombocytopenia. The acute mortality of variceal bleeding ranges from 8% to 30% and the risk of rebleeding is even higher. Patients with varices tend to be chronically ill with impaired hemostatic, immune, and renal functions, so it is not surprising that these patients often die within 12 months of the first bleeding episode.
Table 37-3. Causes of Portal Hypertension

<table>
<thead>
<tr>
<th>Prehepatic</th>
<th>Intrahepatic</th>
<th>Sinusoidal</th>
<th>Posthepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal vein thrombosis</td>
<td>Schistosomiasis</td>
<td>Cirrhosis</td>
<td>Budd-Chiari syndrome</td>
</tr>
<tr>
<td>Congenital</td>
<td>Sarcoidosis</td>
<td>Veno-occlusive disease</td>
<td>Right heart failure</td>
</tr>
<tr>
<td>Septic</td>
<td>Graft vs. host disease</td>
<td></td>
<td>Constrictive pericarditis</td>
</tr>
<tr>
<td>Traumatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
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<td></td>
</tr>
</tbody>
</table>

Because many bleeding episodes in patients with esophageal varices originate from nonvariceal sources (e.g., ulcers, gastritis), it is important to identify the bleeding site before initiating definitive therapy. As with all massive GI bleeding, fluid resuscitation, Hgb maintenance, and correction of coagulation abnormalities are key components of therapy. For patients with variceal bleeding, some clinicians preferentially use vasopressors over fluid replacement, theorizing that the hepatic vein/portal pressure gradient will be reduced and, thus, the risk of hemorrhage will be lowered. Unfortunately, no human data exist to support this contention, and volume depletion can result in hypoperfusion of other organs. The accumulation of massive ascites can contribute to an increased hepatic vein/portal vein pressure gradient. Therefore, for some patients, large-volume paracentesis can be a useful adjunct to reduce the driving pressure for hemorrhage. There is no evidence that gentle gastric tube insertion aggravates variceal bleeding; however, such tubes may promote esophagitis, acid reflux, and gastric erosion if left in place for prolonged periods. Aspiration pneumonitis is extremely common among patients with variceal bleeding because of depressed mental status, massive vomiting, and esophageal instrumentation. Hence, for many patients, early “prophylactic” endotracheal intubation is reasonable.

After airway and circulatory stability have been achieved and variceal bleeding is confirmed, five methods are available to control the bleeding: pharmacotherapy, variceal tamponade, variceal obliteration, decompressive shunting, and liver transplantation. One commonly used plan to gain control of variceal hemorrhage is outlined in Figure 37-4.

**Pharmacotherapy**

Octreotide, a routinely administered splanchnic vasoconstrictor, also inhibits the release of gastrointestinal hormones. Virtually all patients receive a PPI along with prophylactic antibiotics, which in this setting have been shown to decrease mortality, hospitalization, rebleeding, bacteremia, spontaneous bacterial peritonitis, and ICU-related infections of the lung and urinary tract. No specific antibiotic regimen has been recommended over another, but third-generation cephalosporins are often employed. In comparative trials, octreotide is as effective as sclerotherapy or banding and is superior to vasopressin or balloon tamponade for halting acute variceal blood loss and in preventing rebleeding. When octreotide (25 to 50 μg/h IV for 2 to 5 days) is added to endoscopic sclerotherapy, the rate of rebleeding is further reduced. Even though octreotide decreases renal perfusion,
The long-used splanchnic vasoconstrictor, often (approx. 50%) gains initial control of variceal bleeding by portal blood flow through collateral vascular channels, but has not been shown to lower the incidence of rebleeding or reduce mortality. If used, the dose is a continuous IV infusion of 0.2 to 0.8 units/min, until 24 hours after bleeding has stopped. (NB: Doses for variceal bleeding are 5 to 20 times those used for septic shock.) Vasopressin is now rarely used for this indication because up to 10% of patients will have
potentially lethal side effects including arrhythmias (especially bradycardia), myocardial and mesenteric ischemia, congestive heart failure, stroke, and renal insufficiency. The addition of nitroglycerin to vasopressin improves the success rate of bleeding control and reduces the risk of vasopressin-induced complications. (In this setting, nitroglycerin is given by constant intravenous infusion at a starting dose of 40 μg/min and titrated to reduce systolic blood pressure to 90 to 100 mm Hg.)

β-blockade has been used to decrease portal blood flow and portal pressure, reducing the risk of variceal rebleeding by as much as 50% during the first year of therapy. Because β-blockers blunt compensatory cardiovascular responses to hemorrhage, they should not be used to treat active variceal bleeding.

**Variceal Tamponade**

Balloon tamponade may be considered to control esophageal bleeding in patients refractory to other modalities. Because tamponade can only be used for 2 to 3 days before it causes tissue necrosis and because half of all patients treated by tamponade rebleed upon balloon deflation, a definitive plan must be devised at the time the tube is inserted. Currently, a four-lumen device with gastric and esophageal balloons (e.g., Minnesota tube) is preferred over the three-lumen Sengstaken-Blakemore tube because it enables the evacuation of the proximal esophagus, thereby reducing the high aspiration risk. Because patients considered for balloon tamponade are hemodynamically unstable, often have altered mental status, and are predisposed to aspiration, they should undergo endotracheal intubation prior to placement. During intubation and Minnesota tube placement, a gown, gloves, mask, and eye protection should be worn because many of these patients are infected with transmissible hepatitis-causing viruses.

The Minnesota tube is inserted through the mouth into the stomach. (Nasal passage is difficult, often causes bleeding, and always causes sinusitis.) Appropriate positioning of the gastric balloon is then checked by radiograph before inflation to prevent potentially fatal esophageal rupture. In emergent situations, the tube may be passed a minimum of 50 cm before the gastric balloon is inflated by 100 mL. Ultrasonic confirmation is reassuring, whereas patient discomfort indicates potential esophageal positioning. If the 100-mL gastric balloon inflation is well tolerated, the balloon should be inflated to 400 to 450 mL (again, after ultrasonic confirmation) and then placed on gentle traction against the gastroesophageal junction. (Tension usually is maintained by securing the tube to a bridle or football helmet placed on the patient.) For the novice, placing traction on the inflated gastric balloon is often a terrifying experience as a huge placenta-like mass of clot, and liquid blood is expelled from the mouth. This event should not be misinterpreted as worsening hemorrhage. The esophageal balloon should be inflated only if bleeding continues with the gastric balloon inflated and then only to a maximum pressure of 40 mm Hg. After completion of this inflation sequence, it is important to confirm the proper configuration by radiograph. The tube should be kept in place for at least 24 hours after cessation of bleeding but no longer than 72 hours. Without meticulous technique and monitoring, complications occur in a high percentage of patients. Aspiration remains the most frequent complication despite recent modifications of tube design. Cephalad migration may produce upper airway obstruction, a catastrophic event for the patient whose airway is unsecured. (Scissors should be kept at the bedside for immediate tube transection and deflation.) Esophagogastric rupture, another devastating complication, usually results from improper tube placement and inflation of the gastric balloon in the esophagus. Pressure necrosis of the nose, mouth, and gastroesophageal mucosa also is common. Because balloon tamponade is cumbersome, dangerous, and less effective than alternative therapies, these interventions are now made infrequently and only as “last-ditch” efforts to stanch otherwise uncontrollable bleeding.

**Variceal Obliteration**

EGD with variceal banding or injection sclerotherapy has become the procedure of choice for variceal bleeding
because it at least temporarily controls hemorrhage in more than 90% of cases and is less dangerous than emergent surgical shunting. Unfortunately, sclerotherapy and banding generally are not effective for gastric varices. In addition, almost all patients undergoing sclerotherapy or banding eventually will rebleed unless repeated procedures are performed until all varices are obliterated or a decompressive intervention follows (see below). When endoscopic ligation (banding) is performed, constrictive elastic bands are placed around the bases of the varices, causing thrombosis. For many endoscopists, banding is the preferred method to occlude varices because it is more effective than sclerotherapy and produces fewer complications. On the other hand, banding is technically more difficult for actively bleeding patients and, once in place, bands may slip off.

During sclerotherapy, varices or the surrounding tissue is injected with a chemical causing rapid thrombosis and long-term scarring. Following sclerotherapy, minor complications (fever, chest pain, and tachycardia) may occur. Major complications occur including (1) aspiration; (2) pulmonary dysfunction (acute respiratory distress syndrome) secondary to aspiration, sepsis, or sclerosants; and (3) local esophageal problems, including ulceration, perforation, stricture, dysmotility, and abscess formation. A rare complication, esophageal perforation, may produce empyema, mediastinitis, or mediastinal hematoma. Occasionally, sclerotherapy incites clinically significant bacteremia. Although banding shares the risk of aspiration and the potential for late esophageal stricture, the dangers of injection-induced infection or sclerosant toxicity are avoided.

**Decompressive Shunting**

Radiological options designed to control variceal bleeding by lowering the hepatic-portal vein pressure gradient have now largely supplanted surgical approaches. Decompressive shunts that target GI bleeding are best reserved for patients with good hepatic parenchymal function considered to be future candidates for transplantation. No shunting procedure improves hepatic function; therefore, shunts do not change ultimate outcome for patients with severely impaired livers. The most widely used option is the transjugular intrahepatic portosystemic shunt (TIPS). In this procedure, a needle is directed from the hepatic vein into the portal vein, and a guidewire is passed through it. After successive dilation, a stent is then slipped over the guidewire, decreasing the portohepatic vein pressure gradient and lowering the pressure within gastroesophageal varices (see illustration, Chapter 11). (Obviously, TIPS cannot relieve the hypertension from portal vein thrombosis.) Often, the varices are reimaged after shunt placement. With patency confirmed, the varices may then be embolized in hopes of reducing the rebleeding. Few data suggest that TIPS reduces ascites or hepatic hydrothorax or improves the hepatorenal syndrome. Potential complications include contrast-induced renal injury, hemorrhage, liver capsule rupture, hemolytic anemia, worsening of hepatic encephalopathy, and death (<2%). Patency of TIPS has improved since the introduction of coated stents. Radiological revision of occluded shunts can usually be attempted. When TIPS blockage is suspected, complete occlusion can be identified by absence of flow on Doppler ultrasound. However, accurately quantifying the pressure gradient across the shunt can only be confirmed by catheterization. Although TIPS may stem bleeding in high-risk patients who are not amenable or responsive to banding or sclerotherapy, it is probably best viewed as a “bridge” to liver transplant, not a definitive remedy for portal hypertension.

Surgical shunts may be classified as total or “selective,” based on the proportion of portal blood flow around the liver. Total shunts, such as portocaval and mesocaval shunts, provide a decompressive anastomosis of a portion of the portal vein to the inferior vena cava. The size and position of the anastomosed vessels determine the vascular pressure and blood flow through the liver. When large, shunts divert nearly all portal blood flow, resulting in a high risk of hepatic encephalopathy and liver failure. Smaller shunts reduce this risk but may fail to lower the portohepatic gradient sufficiently to avert bleeding. More selective procedures, such as the distal splenorenal shunt, decompress portal circulation by joining the splenic and left renal vein. Selective shunts better preserve hepatic perfusion while decreasing portal pressure and varix diameter, thereby reducing bleeding risk. In experienced centers, selective shunts are still occasionally used for elective decompression but are time
long-term survival; however, they do change the cause of death from GI hemorrhage to encephalopathy and liver failure. Surgical shunting procedures do not preclude subsequent liver transplantation. With the increasing effectiveness of endoscopic therapy and the use of TIPS procedures as a bridge to hepatic transplantation, surgical shunts are seldom performed.

Liver Transplant
Although liver transplantation corrects portal hypertension, the primary indication for transplantation is parenchymal hepatic failure, not variceal bleeding. Patients with more severe parenchymal disease who lack other contraindications may be considered for liver transplant. Liver transplantation is a complex and expensive procedure that carries significant risks for primary graft failure (1% to 5%), acute rejection (4 to 14 days after transplant), and infection secondary to the required immunosuppression. Bacterial infections of the abdomen and lung are most common problem in the first 4 to 6 weeks, although vigilance must be maintained for fungal, especially candidal, infections. The incidence of cytomegalovirus infections rises in frequency to a peak near the end of the first month and can be reduced by ganciclovir prophylaxis.

Aortoenteric Fistulas
On rare occasion, abdominal aortic aneurysms or prosthetic aortic grafts may erode into the GI tract, causing massive hemorrhage (Fig. 37-5). The most common scenario is erosion into the duodenum of the suture line from a previously placed aortic graft. Exsanguination often follows a moderate to large “herald” bleed that stops spontaneously. Aortoenteric fistulas usually occur in the distal duodenum and occasionally cause pulsatile bleeding from the mouth or orogastric tube. Endoscopy, aortography, and contrast CT scanning can establish this diagnosis but frequently are not completed before death. Immediate laparotomy should be undertaken in patients with a confirmed diagnosis or intractable bleeding otherwise unexplained in a predisposed patient.

FIGURE 37-5. Aortoenteric fistula with vascular graft eroded into the jejunum. (From Carlson CJ, O’Keefe GE. Acute gastrointestinal hemorrhage. In: Britt LD, Peitzman AB, Barie PS, Jurkovich GJ, eds. Acute Care
Vascular Malformations

Angiodysplasia is the most common form of enteric vascular abnormality, a category that also includes arteriovenous malformations and vascular telangiectasia. Although angiodysplasia occurs most commonly in the large bowel, it also causes UGI bleeding in patients with aortic stenosis and von Willebrand disease and is second only to erosive gastritis as a source of bleeding in patients with renal failure. Most microvascular malformations involving the UGI tract are located in the duodenum. The diagnosis must be made by angiography or by EGD. (Confirming a EGD diagnosis can be difficult because of the small size of most of these lesions, but when located, they can be ablated by thermal coagulation.)

Miscellaneous Causes

Hemobilia, a rare cause of UGI bleeding, occurs when hepatic blood drains via the bile ducts into the duodenum. The triad of abdominal pain, jaundice, and UGI bleeding should prompt consideration of this condition. Hemobilia may result from pancreatitis, or tumor involvement of the bile ducts or liver, but most commonly follows blunt chest or abdominal trauma. (Recent ERCP can also cause such bleeding.) Fortunately, hemobilia is seldom massive and spontaneously resolves in most cases.

Although acute pancreatitis is an unusual primary cause of UGI bleeding, hemorrhage may occur when pseudocysts or pancreatic tumors erode the posterior duodenal wall. Much more often, patients with acute pancreatitis bleed from gastritis, ulcers, Mallory-Weiss tears, or esophageal unrelated to pancreatic inflammation itself.

Surgical Intervention

Unfortunately, those bleeding patients most in need of surgery often are the worst operative candidates because of their limited tolerance of anemia and hypotension. For patients with ulcer-related UGI bleeding who are not good surgical candidates, consideration should be given to multiple sessions of endoscopic injection of epinephrine and/or thermal coagulation. Angiography with embolization also may be helpful if anesthesia must be avoided. Several indications prompt surgical intervention in UGI bleeding: (1) a visible or spurting vessel in the base of an ulcer crater, even if initially controlled by nonsurgical means; (2) brisk hemorrhage from a lesion that perforates a viscus; and (3) massive ongoing blood losses from any source (>1,500 mL or 6 to 10 units of blood in the first 24 hours).

Prognosis

Regardless of source, several clinical factors predicting a poor prognosis have been identified for patients with UGI bleeding: large hemorrhage, coagulopathy, bleeding from an obscure site, advanced age, or presence of multiple organ failures. Specifically, the combination of renal failure and hepatic parenchymal failure carries a dismal prognosis. In addition, specific upper tract endoscopic findings have also been shown to predict the risk of rebleeding as has been discussed above.

LOWER GASTROINTESTINAL (LGI) BLEEDING

Lower gastrointestinal hemorrhage tends to be intermittent and less profuse than upper GI bleeding. Because bleeding can arise from a much larger anatomic area, the source is often more difficult to diagnose. The most common causes of significant LGI bleeding are shown in Table 37-4. Several points deserve emphasis: a
significant proportion of “lower GI” bleeding actually is the result of blood flowing downstream from an UGI source. This is in distinct contrast to UGI bleeding, which essentially never arises from the lower tract. Diverticular bleeding (30% to 50%) and angiodysplasia (20% to 30%) lead the list of bleeding sources, being almost twice as likely as the next most common etiologies, colitis, neoplasm, and polyps. In contrast to UGI hemorrhage, which almost always is accurately and rapidly diagnosed, the source of LGI bleeding remains undiagnosed in approximately 10% of patients. Luckily, most LGI bleeding episodes (nearly 80%) spontaneously cease. Unfortunately, rebleeding occurs in as many as 25% of patients.

Table 37-4. Causes of LGI Bleeding

<table>
<thead>
<tr>
<th>Condition</th>
<th>Approximate Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diverticular disease</td>
<td>40%</td>
</tr>
<tr>
<td>Angiodysplasia</td>
<td>30%</td>
</tr>
<tr>
<td>Ischemic and inflammatory colitis</td>
<td>5%</td>
</tr>
<tr>
<td>Polyps—carcinoma</td>
<td>5%</td>
</tr>
<tr>
<td>Other—miscellaneous</td>
<td>5%</td>
</tr>
<tr>
<td>Unknown</td>
<td>10%</td>
</tr>
<tr>
<td>Upper GI source</td>
<td>10%</td>
</tr>
</tbody>
</table>

The Diagnostic Approach

The diagnostic evaluation of LGI bleeding is significantly more complex than that for UGI hemorrhage. A suggested schema for the evaluation of LGI bleeding is presented in Figure 37-6, and specific diagnostic tests are discussed below.

**Barium Studies**

Barium studies currently have no role in diagnosing LGI bleeding. Barium enema cannot visualize angiodysplasia or colitis, and even when diverticuli or cancerous lesions are seen, there is no confirmation they are bleeding. Furthermore, filling the colon with barium complicates subsequent angiographic, endoscopic, and surgical interventions.

**Colonoscopy**

When feasible, colonoscopy performed after thorough bowel preparation (e.g., purging with polyethylene glycol) is the diagnostic procedure with the highest yield (70% to 80%), and if not diagnostic, does not prevent subsequent diagnostic attempts. Colonoscopy can be safely performed at the bedside and offers therapeutic options. Regrettably, inadequate preparation before emergent colonoscopy often precludes an adequate examination and increases risk of perforation. Optimal timing of colonoscopy is debated. Even though studies performed early have higher diagnostic rates, speed does not translate into reductions in rebleeding, transfusion,
length of stay, or mortality. Hence, colonoscopy is probably best performed after hemodynamic stabilization and as soon as a bowel prep can be completed. If no diagnosis is reached after colonoscopy and bleeding continues or recurs, a nuclear medicine scan or angiogram should be considered.

**FIGURE 37-6. Suggested evaluation of suspected lower GI bleeding.** When history and physical examination suggest lower GI bleeding is likely, the diagnostic sequence is often dictated by the rate of bleeding. When bleeding is slow, a thorough bowel preparation followed by colonoscopy is most likely to yield a diagnosis. When bleeding is brisk, angiography and tagged RBC scanning are often diagnostic if colonoscopy fails. TSC, technetium scan.

**GI Bleeding Scans**

Two types of nuclear bleeding scans are in common use: technetium sulfur colloid and technetium-labeled (“tagged”) red blood cells. In both tests, the abdomen is scanned to look for “puddling” of radioactive tracer. After injection of the short-lived technetium sulfur colloid, signal can be seen in the bowel even with bleeding rates as...
low as 0.1 mL/min. Although highly sensitive, the short duration of the tracer often misses intermittently bleeding lesions. This problem is lessened with the tagged cell study in which the patient's red blood cells are labeled ex vivo with technetium-99m and then reinjected. The long half-life of tagged RBCs permits repeated scanning for up to 24 hours, a feature particularly useful in patients with intermittent bleeding. Although the technique is more sensitive than angiography, it suggests a bleeding site in only one quarter of cases. What is more worrisome is that about 25% of these results are false positives. Most studies that will ever be positive are diagnostic within minutes, but repeated imaging up to 18 hours may be required. A significant disadvantage is that each scan must be done in the radiology department incurring transport risks and costs. Imprecision is the major problem with radionuclide scanning: the general region of bleeding may be identified, but precise localization requires endoscopy or arteriography. A major advantage of nuclear scans, however, is that no bowel preparation is necessary.

Although a rare problem, Meckel diverticuli may be localized using a radioactive tracer secreted by ectopic gastric mucosa within the diverticulum. Although highly sensitive and specific, false-positive scans are seen in nonfasting patients and in those with large arteriovenous malformations.

### Angiography

A diagnostic angiogram requires a skilled radiologist, a cooperative patient, and a rapidly bleeding lesion. To demonstrate contrast extravasation, patients must be bleeding at a rate exceeding 0.5 mL/min. A nuclear scan before angiography may serve two uses. First, if the highly sensitive nuclear scan is negative, performing angiography is likely to be futile. Second, results help guide the angiographer to the most likely region of bleeding. Theoretically, this approach helps reduce the time to perform the procedure and the required dye load. When there is no guiding information, first injecting the superior mesenteric artery is logical because most diverticular bleeding and all bleeding from angiodysplasia occur in this vascular distribution. If negative, injection of the inferior mesenteric and celiac arteries follows. Success rates for detection of bleeding sites vary widely, depending on patient characteristics, the angiographer's experience, and the source of bleeding. Advantages of angiography include the precise localization of bleeding, the ability to be performed on the unprepared bowel, and the option of injecting vasoconstrictors or embolization for control.

### Specific Conditions and Causes of LGI Bleeding

#### Diverticulosis

Diverticulosis is a disease of patients over the age of 40 years and is responsible for about 30% to 50% of significant LGI bleeding episodes. Diverticular bleeding is sudden in onset, painless in nature, and usually self-limited, but it recurs in 10% to 25% of patients. Interestingly, diverticular bleeding does not typically occur in patients with acute diverticulitis (characterized by fever and lower abdominal pain). The value of colonoscopy is usually compromised by large amounts of colonic blood and stool in the unprepared patient. The detection rate of tagged RBC studies varies with the severity of bleeding, but even when localized to the colon, such studies do not distinguish between diverticular disease and angiodysplasia. Angiography demonstrates the site of active bleeding in one half to three quarters of cases and offers the therapeutic option of intra-arterial vasoconstrictor infusion or embolization.

#### Angiodysplasia

Angiodysplasia is largely a disease of the elderly. Most angiodysplasia lesions never bleed and are incidental findings at the time of colonoscopy. There are no unique historical features that distinguish angiodysplastic from diverticular bleeding. However, the venous bleeding of angiodysplasia is usually less severe than the arterial bleeding of diverticulosis. Like diverticular bleeding, angiodysplastic bleeding almost always spontaneously
stops, but recurs even more commonly (25% to 50%). Colonoscopy can detect bleeding angiodysplastic lesions in 70% to 80% of cases when the colon is optimally prepared. Angiography less reliably displays vascular malformations (35% to 70%) and confirms hemorrhage much less often. Because of the high incidence of rebleeding, endoscopic thermal coagulation or injection or surgical removal of the involved portion of colon should be considered if hemorrhaging angiodysplastic vessels are demonstrated.

**Polyps and Colon Carcinoma**

Colon carcinoma more commonly produces slow, continuous blood loss than massive GI hemorrhage. Left colonic and rectal neoplasms are most likely to cause gross bleeding. Premonitory symptoms include a change in bowel habits, melena, and crampy abdominal pain, with or without weight loss. Rectal examination followed by colonoscopy is likely to reveal the cancerous site of blood loss.

**Other Causes of LGI Bleeding**

Ischemic colitis and bowel infarction from mesenteric thrombosis or embolism may produce mucosal sloughing, bowel necrosis, and LGI bleeding (see Chapter 36). Significant blood loss in ischemic colitis is unusual, and most episodes stop spontaneously (Fig. 37-7). The splenic flexure and descending colon are the most commonly affected sites. Inflammatory bowel disease may cause massive LGI bleeding in the young. In such patients, bloody diarrhea is commonly superimposed on chronic, crampy abdominal pain. The diagnosis is made by colonoscopy and therapy is medical, unless massive persistent hemorrhage necessitates colectomy. Rectal ulcers are another rare but potentially fatal cause of massive LGI bleeding occurring most frequently in patients with chronic renal failure. Rectal varices can produce massive hematochezia in patients with portal hypertension.

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LGI Bleeding Therapy

Only a small minority (approx. 20%) of patients with LGI bleeding need any intervention to stop blood loss. Colonoscopy using thermal coagulation can almost always stop bleeding that follows polypectomy, usually stops the bleeding of angiodysplasia, and occasionally controls the bleeding of diverticulosis. Potential complications include perforation and exacerbation of the bleeding.

Angiographic techniques to stop LGI bleeding include intra-arterial vasoconstrictor infusion and embolization. Vasoconstrictors are effective in approximately 90% of episodes of angiodysplasia or diverticulosis. Such therapy leads to a 5% to 15% complication rate and about a 50% incidence of rebleeding. In nonsurgical candidates who fail vasoconstrictors, distal embolization using small coagulating plugs (e.g., “gel-foam”) may terminate bleeding. Embolization carries about a 20% risk of infarction. Because of the high incidence of rebleeding in angiodysplasia, however, resection is often recommended.

In patients with massive LGI bleeding of undetermined origin, exploratory laparotomy is usually ill-advised because it identifies the site in only one third of cases. If the bleeding site cannot be found at the time of laparotomy, a right hemicolecctomy is usually performed because both bleeding diverticuli and angiodysplastic lesions are more common there. Emergent blind segmental resection of the colon is associated with a mortality rate of 30% to 40% and a similar chance of rebleeding. Localization of the bleeding site by angiography or colonoscopy reduces mortality risk to less than 10% and minimizes the risk of rebleeding. Because of the operative risks of emergent colectomy, resection should be considered only for patients with massive bleeding who fail angiography and embolization, patients with numerous angiodysplastic lesions, and patients with angiodysplasia who fail thermal coagulation therapy.

SUGGESTED READINGS


**Chapter 38**

**Burns and Inhalation Injury**

- **Key Points**

1. For burn victims, the keystones of initial therapy are crystalloid resuscitation and management of smoke inhalation. Isotonic crystalloid (scaled to percentage of body surface area burned) is required for volume resuscitation during the first 24 hours after the injury.

2. Carbon monoxide and cyanide poisoning should be considered in the setting of inhalation injury. The role of hyperbaric oxygen therapy for carbon monoxide poisoning remains controversial and is best limited to comatose patients with high carbon monoxide-hemoglobin levels who can be treated promptly. Antidotes are available for cyanide, and these should be considered for patients with unexplained metabolic acidosis persisting after apparently adequate resuscitation.

3. The hypermetabolic state and compartmental fluid shifts often dramatically alter drug therapy in the burned patient. In many cases, drug doses must be significantly increased to achieve therapeutic effect.

4. Burn patients require significant metabolic support to meet the physical demands of injury. Temperature, minute ventilation, and cardiac output are increased. Aggressive nutritional and respiratory support is essential in these patients.

**PATHOPHYSIOLOGY**

In serious burns, some tissue is immediately lost to direct thermal injury. Adjoining regions that are sublethally injured may be even more important to dysfunction, as they serve as an engine for inflammation. The tissue bordering a major burn generates inflammatory products, oxidants, and lipid mediators that act locally and systemically to increase vascular permeability, promote thrombosis, and depress cardiovascular function. These changes result in the familiar clinical findings of fever, leukocytosis, and increased vascular permeability that manifest as hypoproteinemia, edema, and hypovolemia. The “watershed” tissue bordering an acute burn is in jeopardy for additional damage from systemic hypoxia, ischemia due to localized clotting and increased tissue pressure, and infection. Thus, prompt reperfusion of these endangered areas is vital to optimal outcome.

**BURN EVALUATION**

Mortality rates for burn victims vary widely, depending on the depth and size of the burn, the patient’s underlying health and age, and the severity of any associated inhalation injury. Most early deaths from fires result from smoke inhalation, which may prove fatal before patients reach the hospital—emphasizing the importance of smoke detection devices. On reaching the hospital, hypovolemic shock secondary to fluid shifts and smoke-induced airflow obstruction are prominent early problems; sepsis is the most common late fatal complication. Inhalation injury is a major determinant of outcome; its presence may double the mortality rate of a burn of any given extent. Not surprisingly, age also is a powerful predictor of mortality. After the airway has been secured and hemodynamics have stabilized, the patient should be examined carefully to determine the depth and extent of thermal injury, and the burns should be gently washed and dressed. An appropriate examination should be conducted to look for associated traumatic injuries, especially if the burn results from an explosion or motor
Estimation of Burn Size and Severity

Burns are classified by partial- or full-thickness destruction or by depth of injury (first to fourth degree) (Table 38-1). In adults, the percentage of body surface affected by burn injury can be estimated by the “rule of nines.” This rule assigns percentages of the total body surface area (TBSA) to the anterior and posterior surfaces of the head, limbs, and trunk

(Fig. 38-1). Determination of the TBSA burned comes from areas involved in second- and third-degree injury. Representative images and skin diagram are given in Figures 38-2 and 38-3. As another useful measure, the palm of the adult hand approximates 1% of TBSA. In children, the Lund-Browder chart is used for estimating the extent of the burn because their heads contribute a disproportionately large proportion of body surface. Estimation of the total area involved by full-thickness burns is useful in determining fluid requirements, need for specialized burn unit care, and expected mortality. However, precise grading of burn wound depth is not essential for the nonburn specialist; in most cases, it is reasonable to regard any burn more extensive than superficial as serious, particularly if it covers ≥10% of the body. Adults with extensive or severe burns and most burned children require hospitalization. Commonly accepted criteria for hospital admission are listed in Table 38-2.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Skin Examination</th>
<th>Sensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>First⁹</td>
<td>Erythema</td>
<td>Painful</td>
</tr>
<tr>
<td>Second⁹</td>
<td>Erythema/blisters/edema</td>
<td>Painful</td>
</tr>
<tr>
<td>Third⁹</td>
<td>White or charred</td>
<td>Anesthetic</td>
</tr>
<tr>
<td></td>
<td>Firmly indurated</td>
<td></td>
</tr>
<tr>
<td>Fourth⁹</td>
<td>Destruction of muscle, fascia, bone</td>
<td>Anesthetic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

⁹Partial thickness.

⁹Full thickness.

Table 38-1. Classification of Burns by Severity
FIGURE 38-1. Burn wound diagram illustrating the surface area of selected body regions. Numbers correspond to percentages of TBSA. The hand is 1% TBSA. (This may be helpful to measure irregular injuries.)
INITIAL MANAGEMENT

Initial management of the patient with severe burns should include a careful assessment of the airway and vital signs to ensure adequate ventilation and perfusion. If carbon monoxide (CO) poisoning is suspected, it is reasonable to obtain a blood sample for CO content and simultaneously to administer 100% oxygen to accelerate its clearance. Immediately after securing the airway and ensuring oxygenation, repletion of circulating volume should be undertaken; hypovolemic shock is the most common cause of death within the first 24 hours after admission.
FIGURE 38-3. Representative photos of first- (A), second- (B and C), and third-degree (D) burns.

Table 38-2. Criteria for Burn Center Referral

<table>
<thead>
<tr>
<th>Burns totaling &gt;20%-25% TBSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-thickness burn &gt;5%-10% TBSA, especially in patients &lt;10 or &gt;50 years</td>
</tr>
<tr>
<td>Burn of a lesser extent accompanied by complicating medical conditions</td>
</tr>
<tr>
<td>Inhalation injury</td>
</tr>
<tr>
<td>Circumferential burns of the trunk or extremities</td>
</tr>
<tr>
<td>Burns of the hand, face, feet, genitals, or perineum</td>
</tr>
</tbody>
</table>
The optimal endpoints for circulatory resuscitation and how to achieve these goals remain controversial. Many intensivists rely on the traditional indicators of heart rate, blood pressure, and urine output, but it has been claimed that some patients remain underresuscitated using these measures. When adequacy of intravascular filling is in doubt, assessment of central venous pressure (CVP) dynamics, central venous oximetry, and ultrasonic evaluation of the heart and great vessels can be helpful. Assessing cardiac performance on an ongoing basis using a Swan-Ganz catheter could be considered in patients with suspected underlying cardiac impairment; in severe burns, CVP alone may not provide sufficient information about left ventricular function (see Chapter 3).

### Fluid Therapy

Burns cause hypovolemia as a result of massive shifts of fluid from intravascular to extravascular compartments and by exudation through injured skin. Hemoconcentration (because of intravascular fluid losses) occurs early, but hemodilution is more likely after appropriate fluid resuscitation. Because the hematocrit can change in either direction, it should be checked regularly during resuscitation with a traditional target being ≥30%. Central venous catheterization may be necessary to deliver the volume of fluid required for adequate resuscitation, and such catheters should be placed though unburned skin whenever possible to minimize the risk of subsequent catheter or wound-related sepsis.

Historically, three strategies (Evans, Brooke, and Parkland) for replacing circulating volume have been recommended. Current practice reduces fluid volume use and standardizes prehospital fluids (Table 38-3). A central feature of all three plans is to administer substantial volumes of salt-containing (Ringer lactate) fluid during the initial 24 hours after injury. Resuscitation requires hourly evaluation of the patient with the overall goal of gradual deescalation of IV fluid rate during the first 24 hours provided that the urine output goal (0.5-1 ml/hr) is met. Customarily, one half of the fluid deficit is replaced in the first 8 hours, with the remainder administered over the next 16 hours. However, patients with concomitant inhalation injury or electrical injury causing myoglobin to appear in the urine, may require more fluid for successful resuscitation. A traditional fluidreplacement target has been to achieve 0.5 to 1 mL/kg/h of urine output in the adult. It is now recognized that in a substantial number (perhaps half) of cases, too much volume is administered. One clinical clue to excessive fluid infusion is a urine output consistently exceeding 2 mL/kg/h. Risks of excessive fluid administration include limb and abdominal compartment syndromes (ACS). Although attention to all injured compartments is strongly advised, ACS is sufficiently common to warrant monitoring of bladder pressure in patients undergoing large and rapid volume resuscitation. All fluid-replacement strategies are associated with the development of tissue edema due to capillary leak, both in burned and unburned tissue. In mass casualty situations, in patients with smaller burns, and when intravenous therapy may not be feasible, oral rehydrating solution may be useful. Following fluid replacement, vasopressors may be needed to maintain adequate cardiac output, blood pressure, and urine flow. High doses of α-adrenergic agonists (e.g., norepinephrine, phenylephrine) should be avoided, if possible, because of their tendency to decrease nutritive blood flow to already injured tissue.

### Table 38-3. Burn Resuscitation in the Adult—First 24 Hours

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Fluid (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>35-45 mL/kg</td>
</tr>
<tr>
<td>5-8</td>
<td>20-30 mL/kg</td>
</tr>
<tr>
<td>9-12</td>
<td>10-20 mL/kg</td>
</tr>
<tr>
<td>13-24</td>
<td>5-10 mL/kg</td>
</tr>
</tbody>
</table>

*a Modified from the American Burn Association Guidelines.*
Prehospital (all)  500 mL LR/h

Thermal and Chemical Burns  2 mL LR/kg/% TBSA 2° and 3° injury with half infused over the first 8 h

High Voltage Electrical Injury with Myoglobinuria  4 mL LR/kg/% TBSA 2° and 3° injury with half infused over the first 8 h

*Times are based on time of injury.

LR, lactated Ringer; TBSA, total body surface area.

After 24 hours, sodium requirements decline and permeability of leaky capillaries decreases. Free water and colloid are then administered in larger quantities to maintain circulating volume and electrolyte balance. After the first 24 hours, evaporative water losses may be estimated by the following formula: hourly water loss (in mL) = \((25 + \% \text{ area of burn}) \times (\text{total TBSA in m}^2)\). This formula predicts that a patient with a 25% burn and a 2-m² BSA will lose approximately 100 mL of water per hour. This formula provides the basis for the common recommendation in both the Brooke and Evans fluid strategies to administer roughly 2 L of free water daily. Within the first 12 hours of the burn event, colloids offer little advantage over crystalloid because the newly injured vasculature fails to retain even the larger colloid molecules. Despite lack of proven benefit, many physicians still administer albumin to decrease the amount of crystalloid used.

**Inhalation Injury**

Respiratory injury resulting from inhalation of smoke or chemical products of combustion is associated with significant morbidity and mortality. The classic risk factor for inhalation injury is the patient trapped in a closed space fire or the individual who loses consciousness and must be rescued from a burning structure. Even in isolation, inhalation injury can be associated with serious and persisting pulmonary dysfunction. Combined with cutaneous burns, inhalation injury increases fluid resuscitation requirements, promotes pulmonary complications, and raises the overall mortality risk of burn injury. Unfortunately, treatment is largely supportive. In most cases, the contributions of inhalation injury and pneumonia to mortality are independent and additive. However, expected mortality in patients with very small or very large burns is not substantially affected by pulmonary complications, except at the extremes of age.

Inhalation injury results from pulmonary trauma caused by inhalation of thermal or chemical irritants. Anatomically, injuries are divided into three classes: heat injury, which is restricted to upper airway structures except in the case of steam jet exposure, chemical irritation (either local or throughout the respiratory tract), and systemic toxicity, such as may occur with inhalation of CO or cyanide (CN).

Respiratory complications are a common cause of early deaths among burn patients. The history and physical examination provide valuable clues to the extent of inhalational injury (Table 38-4). Burns and inhalation injuries cause respiratory complications through five basic physiologic mechanisms: (1) airway obstruction, (2) toxin inhalation, (3) increased metabolism and ventilation requirements, (4) impairment of host defenses, and (5) production of late obstructive and restrictive lung dysfunction.

**Airway Obstruction**

Hot gases, particularly steam (because its heat content is much greater than dry air), can rapidly cause upper
airway injury and bronchospasm; however, heat-related tissue edema can progress for 24 to 48 hours after the injury. Because the upper airway is such an efficient heat sink, it is uncommon to see lower respiratory tract thermal injury unless the patient has been trapped in a closed-space fire, often with superheated gas. Patients with burns of the face or neck that appear inconsequential at the time of admission may quickly experience tissue swelling that leads to life-threatening airway obstruction. Intubation should be considered in patients with significant second and third degree face and neck burns. Failure to follow this principle may lead to situations in which massive tissue swelling eventually precludes airway cannulation. If intubation is required, a large-diameter orotracheal tube should be placed, if possible, to facilitate clearance of secretions and performance of bronchoscopy, should the need arise. In this setting, the endotracheal tube generally should remain in place for at least 72 hours. When patency of the airway is uncertain, laryngoscopy or bronchoscopy can evaluate the severity of airway edema and need for endotracheal intubation. One should err on the side of intubation if there is clinical evidence of airway obstruction or if laryngoscopy demonstrates supraglottic edema. Hypoxemia or diffuse radiographic infiltrates at the time of admission are also poor prognostic signs that indicate the need for early intubation and mechanical ventilation. However, a normal chest radiograph or PaO\textsubscript{2} emphatically does \textit{not} exclude inhalation injury.

<table>
<thead>
<tr>
<th>Clues to Inhalation Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enclosed-space exposure</td>
</tr>
<tr>
<td>Loss of consciousness</td>
</tr>
<tr>
<td>Nasal, oral, or facial burns</td>
</tr>
<tr>
<td>Carbonaceous sputum</td>
</tr>
<tr>
<td>Hoarseness or stridor</td>
</tr>
<tr>
<td>Upper airway changes by bronchoscopy</td>
</tr>
<tr>
<td>Pulmonary edema on chest radiograph</td>
</tr>
</tbody>
</table>

For patients not requiring immediate intubation for airway obstruction or hypoxemia, bronchodilators and humidified oxygen may avert the need for mechanical ventilation. Neither therapy, however, should delay intubation for patients with facial burns or symptomatic airway compromise. Bronchospasm and bronchorrhea commonly develop after inhalation injury to the lower airway. Although effective early on, bronchodilators are of less value later in the course of postburn airway obstruction. Bronchoscopic evaluation of the airway often reveals sloughed mucosa or extractable secretions. Because corticosteroids do not reduce airway edema but do substantially increase mortality by predisposing patients to infection, they should be avoided. Simple measures such as elevating the head of the bed to 30 degrees during initial resuscitation may help to decrease the degree of airway edema. The rate of fluid administration should not be decreased when burns involve the airway; in fact, fluid requirements tend to be increased in the setting of inhalation injury.

**Increased Ventilatory Requirements**

Minute ventilation may be high after large burns because of increased metabolic demands; a 50% to 60% burn may double caloric requirements and CO\textsubscript{2} production. Although hyperpnea usually is due to the burn-induced hypermetabolic state, alternative explanations (e.g., hyperthyroidism, drug or alcohol withdrawal, pneumonia, acute respiratory distress syndrome [ARDS], pulmonary embolism, or uncontrolled pain) should be considered. The increased ventilatory requirements may be sufficient to overwhelm the capability of patients with underlying
l lung disease to meet them, resulting in respiratory failure.

**Toxic Gas Inhalation**

Depending on the fuel consumed, fires may produce numerous noxious compounds that can cause respiratory inflammation and systemic toxicity (Table 38-5). With or without fire, all inhaled gases injure in one of three basic ways: (1) by acting as asphyxiants, (2) by causing airway irritation, or (3) by functioning as systemic toxins. Any gas (e.g., nitrogen, helium, nitrous oxide, carbon dioxide) may be a lethal asphyxiants when it displaces oxygen from the atmosphere or competes with oxygen for hemoglobin, resulting in a hypoxic gas mixture.

Water-soluble gases usually act as immediate irritants because they deposit in high concentrations on the mucous membranes of the moist upper airway. Airway edema and bronchospasm usually result from the high-solubility gases such as chlorine, ammonia, hydrogen chloride, and sulfur dioxide. By contrast, low-solubility toxins (e.g., phosgene and nitrogen dioxide) are more likely to gain deeper access to lung tissues, as are potent acids or aldehydes carried there by inhaled particulates. Obviously, when victims are trapped in a closed space, even highly soluble irritating gases may reach the lower respiratory tract. The injury resulting from lower airway gas exposure is similar to aspiration, presenting as diffuse bronchoconstriction, reduced lung compliance, and mismatching of ventilation and perfusion. Chemical injury is suggested by the exposure history and by the presence of erythema below the vocal cords. The mucosal edema of chemical injury builds for 24 to 48 hours after exposure and severely impairs mucociliary transport. In addition, the inflammatory mediators and white cells released into the airways promote secretion formation, atelectasis development, and ventilation-perfusion mismatching. Copious secretions, bronchospasm, airway obstruction, and ciliary damage warrant suctioning and bronchodilator therapy. In cases of severe inhalation injury, the airway mucosa often sloughs at about 72 hours and requires 7 to 14 days to regenerate. If not recognized, the shed airway lining can precipitate a crisis if it obstructs the airways and the distal orifice of the endotracheal tube. When this happens, typically, *exhalation* is limited resulting in air trapping and auto-PEEP. Endotracheal tube obstruction usually responds to simple suctioning, but bronchoscopy or even tube exchange sometimes is necessary. Bacterial superinfection and pneumonitis are common complications of airway injury.

<table>
<thead>
<tr>
<th>Material Burned</th>
<th>Toxic Product</th>
<th>Physiologic Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood, paper, cotton</td>
<td>Acrolein, acetaldehyde, formaldehyde, acetic acid</td>
<td>Airway irritation, bronchospasm, mucosal sloughing</td>
</tr>
<tr>
<td>Plastics</td>
<td>Phosgene, chlorine Hydrogen chloride</td>
<td>Airway irritation</td>
</tr>
<tr>
<td>Wool, silk</td>
<td>Hydrogen cyanide</td>
<td>Cyanide poisoning, tissue hypoxia</td>
</tr>
<tr>
<td>Synthetic (polyurethane, nylon, rayon)</td>
<td>Hydrogen cyanide Oxides of nitrogen</td>
<td>Cyanide poisoning, tissue hypoxia Pulmonary edema</td>
</tr>
<tr>
<td>All of the above</td>
<td>Carbon monoxide</td>
<td>Tissue hypoxia</td>
</tr>
</tbody>
</table>
Carbon Monoxide and Cyanide

CO and CN are the two most common fire-related inhaled toxins. CO is the primary cause of death in fire fatalities at the scene. CO competes directly with oxygen for hemoglobin binding, fixes to cytochrome oxidase, and displaces the oxyhemoglobin dissociation curve leftward, impairing release of oxygen to the tissues. Because the affinity of CO for hemoglobin is roughly 200 times greater than that of oxygen, even low concentrations of inspired CO can rapidly produce fatally high levels of nonfunctional carboxyhemoglobin (CO-Hgb). The sensitivity of a patient to CO is influenced strongly by underlying health; patients with diseases of the central nervous system or heart are especially vulnerable. The clinical symptoms of acute CO poisoning are those of tissue hypoxia and usually correlate well with the CO-Hgb level (Table 38-6). However, because of the time needed for extrication and transport of victims to the hospital, and the prehospital use of oxygen, CO-Hgb levels may be undetectable at the time of admission. For this reason, low levels of CO-Hgb should not be used as evidence of an absence of CO effect. Even if measurable, the correlation between acute CO-Hgb levels and late neuropsychiatric effects is poor.

Two principles underpin treatment of CO poisoning: maximization of tissue O₂ delivery and use of high concentrations of O₂ to promote CO excretion. While breathing air, the elimination half-life (t½) of CO-Hgb is 2 to 6 hours. When breathing pure O₂ at ambient pressure, the t½ declines to 30 to 90 minutes. Because O₂ profoundly improves CO clearance, the most important therapy in patients with suspected CO poisoning is to immediately administer 100% oxygen. CO-Hgb levels exceeding 25% in normal subjects or 15% in patients with ischemic heart disease should be treated aggressively. High fractions of inspired O₂ should be used until the CO-Hgb concentration falls below 10%.

<table>
<thead>
<tr>
<th>Carboxyhemoglobin Level</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>Usually none</td>
</tr>
<tr>
<td>5%-15%</td>
<td>Mild headache, dyspnea</td>
</tr>
<tr>
<td>15%-20%</td>
<td>Headache, dizziness, confusion, nausea, vomiting</td>
</tr>
<tr>
<td>20%-40%</td>
<td>Disorientation, visual impairment, nausea</td>
</tr>
<tr>
<td>40%-60%</td>
<td>Hallucinations, coma, seizures, shock</td>
</tr>
<tr>
<td>&gt;60%</td>
<td>Death</td>
</tr>
</tbody>
</table>

*Table 38-6. CO-Hgb Levels and Symptoms*[^1]

[^1]: Absence of detectable CO-Hgb does not rule out CO exposure.
The use of hyperbaric oxygen (HBO) remains controversial, and after numerous clinical trials, no consensus has been reached supporting or discouraging its use. Although HBO can further accelerate removal of CO from the body (elimination t½ < 20 minutes), hyperbaric chambers are not widely available and complicate management; it is difficult to provide ongoing burn resuscitation and wound care inside the HBO chamber. HBO may also result in otic barotrauma or seizures. Furthermore, after the first hour, HBO offers little advantage over 100% ambient pressure oxygen in reducing CO-Hgb levels. Taken together, randomized studies do not suggest that the late complications after CO exposure are significantly reduced by HBO. A reasonable compromise is to consider HBO, if locally available, for neurologically symptomatic but otherwise stable victims of CO exposure. Presently, the benefits of HBO do not appear to exceed the risks of transporting acutely ill, unstable patients over long distances to receive the therapy.

Fires also generate CN through the combustion of wood, silk, nylon, and polyurethane. CN binds to tissue cytochromes, impairing O₂ use and causing lactic acidosis. Because specific diagnostic tests are not readily available, CN exposure often goes unrecognized. Hyperbaric O₂ therapy is not useful in CN toxicity because the pathophysiologic defect is in O₂ usage at the cellular level, not one of O₂ delivery. Tissue hypoxia from CO or CN usually is evident immediately after exposure and should be suspected in burn patients with apparently normal clinical indices of perfusion and oxygenation but unexplained metabolic (lactic) acidosis.

In CO poisoning, arterial blood gases may demonstrate a nearly normal PaO₂ but decreased measured O₂ content and measured hemoglobin saturation, as CO displaces O₂ from hemoglobin but not that dissolved in plasma. Because their photometric properties are similar, bedside pulse oximetry cannot distinguish CO-Hgb from normal oxyhemoglobin; that distinction relies on co-oximetry. In CN intoxication, PaO₂ and O₂ saturation and O₂ content may all be normal, and if measured, mixed venous O₂ saturations are unexpectedly high because of underuse of delivered O₂. Thus, CN poisoning usually results in normal, or even high, pulse oximetry saturations. The bottom line is that pulse oximetry cannot reliably detect either CO or CN.

Historically, the treatment of CN poisoning has involved intravenous sodium nitrite to produce methemoglobin, which acts as a sink for CN, displacing it from the intracellular cytochromes. The CN portion of the resulting cyanomethemoglobin is then extracted by the liver enzyme rhodanese and in the presence of sulfur (from intravenous sodium thiosulfate) converted into the relatively nontoxic thiocyanate ion, which is subsequently eliminated by the kidney. 4-Dimethylaminophenol (DMAP) is another compound used for CN poisoning that also works by generating methemoglobinemia. Neither of these treatments is ideal, because the creation of methemoglobin, even transiently, diminishes oxygen carrying capacity. Alternate methods of CN detoxification have been developed to avoid the problem of methemoglobin formation. In some countries, dicobalt edentate has been used, but extreme caution is advised—the diagnosis must be certain, because the therapy itself is toxic in the absence of CN. The newest treatment gaining popularity is hydroxocobalamin. Hydroxocobalamin (5 to 10 g IV) safely chelates CN directly, thereby creating cyanocobalamin, a natural form of vitamin B₁₂, which is excreted in the urine. At present, available data suggest that hydroxocobalamin is the antidote of first choice in CN exposure. Unfortunately, a rapid CN assay is not available to document actual poisoning before antidote administration.

Other Important Considerations

Major burns impair the ability to conserve heat and maintain body temperature. Therefore, after burn cleansing, wounds should be covered with clean, warm coverings and body temperature monitored closely. Failure to prevent hypothermia impairs coagulation and can dramatically increase oxygen requirements if shivering occurs. The reduced mobility, sedation, and tissue edema predispose to deep venous thrombosis (DVT) and pressure
ulcer formation, and thus, consideration should be given to DVT prophylaxis and specialized beds to prevent these dangerous and costly complications. Ileus commonly follows major burns, and gastric distension or markedly diminished bowel sounds should prompt insertion of an oral or nasogastric tube connected to suction. After wound cleansing, a topical antimicrobial should be applied to limit skin colonization by bacteria. Systemic antibiotics offer no demonstrated advantage in prophylaxis. Without confirmation of recent immunization, tetanus toxoid should be administered. Pain and anxiety relief, particularly in partial-thickness burns, is critical to allow debridement, cleansing, and other patient manipulations (see Chapter 17). Full-thickness burns are frequently anesthetic.

COMPLICATIONS OF BURNS
The later complications of burns include (1) infection/sepsis/multiple organ failure, (2) gastrointestinal bleeding, (3) hypermetabolism, and (4) local wound problems.

Infection and Sepsis
Infection is the greatest threat to life of burn patients after the first 36 hours; pneumonia and burn wound sepsis represent the most common and lethal conditions. Immunocompetence of burned patients, including T cell, monocyte, and macrophage function, is significantly depressed. Clearly, nosocomial pneumonitis is an ever-present risk for the intubated patient, particularly when inhalation injury has compromised host defenses (see Chapters 26 and 27).

Devastating infection also can result from skin disruption. Massive numbers of bacteria may invade the burn wound and adjacent tissue. In the first 3 to 5 days after a burn, staphylococci are the most common invading organisms, but after 5 days, gram-negative rods (frequently Pseudomonas) predominate. Later in the course of burn care, invasive fungal infection should be considered when severe sepsis fails to resolve with antibacterial agents. In addition to standard methods of infection control, meticulous wound care, including the use of topical antibiotics, early wound debridement and closure, and use of gowns, masks, and gloves decrease the infection risk. When antibiotics are used in response to demonstrated infection (not prophylaxis), it should be kept in mind that resuscitated burned patients have accelerated clearance of some drugs, most notably aminoglycosides. Increased basal temperature renders the detection of wound infection difficult. Because the temperature of burn patients may rise as high as 38.5°C as a result of hypermetabolism, fever to this degree does not necessarily warrant the institution of antibiotics. When burn wound sepsis is suspected, quantitative cultures of burned tissue should be performed. Growth of more than $10^5$ organisms per gram of tissue or histological evidence of invasion of adjacent unburned skin is highly suggestive of severe complicating infection. Long before the results of these tests are available, however, antibiotics must be instituted on clinical grounds if high spiking fever, leukocytosis, and neutrophilia, or other signs of sepsis, are present.

Even without infection, a significant inflammatory response can result from the burn wound itself (see Chapter 27). The occurrence of severe sepsis and pronounced hypermetabolism is reduced by early burn wound excision and grafting, aggressive nutritional support, and prompt diagnosis and treatment of infections.

Gastrointestinal Bleeding
Gastrointestinal bleeding due to stress (Curling) ulceration once occurred commonly among burn patients but now is seldom encountered. Burn victims are one of the groups to clearly benefit from empiric stress ulceration prophylaxis. Effective prophylaxis includes effective resuscitation, histamine blockers, proton pump inhibitors, and aggressive enteral nutrition that begins soon after admission. With these effective prophylactic measures, the incidence of stress ulceration with associated bleeding has fallen dramatically: less than 5% of patients have
clinically significant ulcers.

**Hypermethabolism and Nutrition**

Extensive burns represent the single greatest sustained metabolic stress experienced by humans. Full expression of hypermethabolism may require 5 to 7 days. Patients with major burns raise resting body temperature and dedicate a large proportion of consumed energy to the heat production that maintains the body's gradient with ambient temperature; therefore, establishing higher environmental temperature reduces caloric expenditure. Adequate nutritional support is essential to patients with significant burns. It is now known that almost all patients can be fed enterally, often within just hours of the injury. The enteral route is preferable because it preserves mucosal integrity, buffers gastric acid, and increases resistance of patients to infection. In the initial phase of treatment, the daily kilocalorie requirement may be roughly estimated as 25 times the weight in kilograms plus 40 times the percentage of TBSA burned. In lieu of estimating caloric requirements, indirect calorimetry can be used to measure caloric expenditure; giving 50% to 60% of the caloric requirement as glucose minimizes catabolic nitrogen losses. Administration of glucose at rates above 5 to 7 mg/kg/min, however, may lead to glucose intolerance and increased CO₂ associated with overfeeding. Lipid may be used as the source for nonprotein calories. Increased lipid clearance observed in burn victims supports the argument for raising the percentage of calories given as fat. It has recently become a common practice to use high-protein (e.g., 2 g/kg body weight) tube feeding preparations. (For a complete discussion of nutrition therapy, see Chapter 16.)

**Burn Wound Care**

Although mastering the care of the burn wound and newer biological dressings extends beyond the skill set of the intensivist who does not subspecialize in such injuries, several basic principles must be understood. The goals of burn wound care are to (1) prevent infection, (2) limit discomfort, (3) accelerate healing, and (4) maximize functional recovery. In general, these goals are best accomplished by the use of early debridement, topical antibiotics, and skin grafting. Topical antimicrobials are applied to the skin once or twice daily to limit wound colonization with bacteria. Wounds should be cleaned and debrided before application of fresh antibiotic, a process often requiring narcotic analgesia. Several topical antibiotics are available, each with unique advantages, antibacterial spectra, and complications (Table 38-7). Silver sulfadiazine is most widely used. Superficial wounds may be managed simply with topical mesh impregnated with a petroleum blend and bismuth tribromophenate possibly in combination with bacitracin. When burn wound sepsis is suspected, empirical antibiotic regimens should cover gramnegative rods including *Pseudomonas aeruginosa* and gram positives including methicillin-resistant *Staphylococcus*.

Many of the same treatment principles that apply to chemical, electrical, and thermal burns are useful for patients with extensive skin damage as the result of toxic epidermal necrolysis or Stevens-Johnson syndrome. Fortunately, such patients rarely require debridement or grafting.

<table>
<thead>
<tr>
<th>Table 38-7. Topical Antimicrobial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Silver Sulfadiazine</strong></td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Mechanical Problems of the Burn Wound

Patients with circumferential burns of the trunk or extremity and those with burns of the face, hands, feet, or perineum require hospital admission and immediate consultation by a burn specialist. Eschar frequently encases the trunk or extremities. These burn wounds may prevent the tissue expansion required to accommodate edema, which reaches maximal severity 12 to 48 hours after injury. Ischemia and/or necrosis from compartment syndrome development may result from the consequent rise of unrelieved tissue pressure. Furthermore, eschar-related limitation of chest expansion may lead to respiratory failure. In the extremities, edema can be minimized by elevating the burned limb. Decreased capillary refill, cyanosis, paresthesia, and deep pain in tissues distal to a circumferential burn site dictate the need for escharotomy. Doppler ultrasound examination demonstrating diminished pulses distal to the circumferential eschar confirms high tissue pressures and potential vascular compromise. In circumferential burns of the trunk, reduced thoracic compliance (noted during mechanical ventilation), severe tachypnea, and ventilatory distress suggest the need for escharotomy.

In general, escharotomy is required when deep second- or third-degree burn injury exists with circumferential orientation. In these releasing procedures, the circumferential wound is usually divided at the lateral aspects of the extremities or, if the burn is truncal, at the flanks, at the subcostal region transversely, and across the suprapubic region to free the anterior abdominal wall (Fig. 38-4). A subcostal incision, an incision across the clavicular region, and incisions in the anterior axillary lines will facilitate respiratory excursion (Fig. 38-5). As noted above, the need for escharotomy becomes clear within 48 hours of injury. Progressive tissue edema during resuscitation often creates the need for escharotomy, even if initial perfusion appears to be adequate. In more extreme cases, laparotomy is sometimes required for ACS with respiratory compromise, as reflected during volume-targeted ventilation by rising peak airway pressure (Figures 38-4 and 38-5).

NONTHERMAL BURNS

Chemical Injury

Copious irrigation with clear water comprises the primary initial treatment of chemical burns of all types. (If the caustic chemical is in a powder form, it makes sense to brush away as much of the material as possible before irrigation.) Care must be taken to avoid extending the chemical injury by allowing the patient to lie in contaminated flush solution. Removal of contaminated clothing and irrigation in a shower are preferable. After flushing, chemical burns should be treated like thermal burns. Although alkaline and acidic chemicals injure tissue by altering its pH, strong neutralizing solutions should not be used because they may precipitate exothermic reactions, risking additional thermal damage. The adequacy of irrigation in pH-related chemical injury may be assessed by testing the area with litmus paper to ensure neutral pH and by inquiry regarding the pain associated with exposure to the chemical.
FIGURE 38-4. Arm featuring escharotomy.
FIGURE 38-5. Preferred sites of escharotomy (dashed and solid lines). Particular care is needed to divide eschar over involved joints (solid lines). (From Pruitt BA, Gamelli RL. Burns. In: Britt LD, Peitzman AB, Barie PS, Jurkovich GJ, eds. Acute Care Surgery. Philadelphia: Lippincott Williams & Wilkins; 2012:446.)

Electrical Burns

Electrical burns inflicted by a high-voltage source may produce extensive internal tissue damage tracking along neurovascular bundles and muscle with little external evidence of injury. Vascular, nerve, and muscle damage occur frequently, and the devitalized tissue is prone to subsequent infection. Electrical injury may cause severe exit wounds at the hands, knees, or feet—sites frequently overlooked in the initial evaluation. (Such wounds are analogous to projectiles, which produce deceptively small entrance lesions but large exit wounds.) Fractures resulting from falls or forceful muscular contraction should be considered in all patients with electrical injuries. For almost all patients with electrical injury, an electrocardiogram should be performed to look for evidence of arrhythmias, myocardial injury, or conduction disturbance. Even if troponin or CK-MB levels are elevated, findings of classical transmural myocardial infarction are rare because epicardial coronary arteries do not become obstructed. Even in the absence of overt cardiac injury, observation in a monitored bed probably is
prudent. Recent data suggest admission may not be necessary for patients with lower-voltage exposures (house current) sustained on dry skin, especially if the electrocardiogram is unremarkable, and there was no evidence of tetany, loss of consciousness, or current flow across the chest. Because of the high incidence of rhabdomyolysis, measurements of CPK and myoglobin should be performed in patients with significant electrical injuries, and if elevated, generous fluid administration in conjunction with osmotic and loop diuretics should be considered to help avert renal failure. A good initial target is a urine output of 1 to 2 mL/kg. Because electrical burns rarely, if ever, require the same degree of fluid administration as do large thermal burns, the use of standardized fluid algorithms is not appropriate for these patients.

SUGGESTED READINGS


Appendix
Definitions and Normal Values

Conversion Factors

TEMPERATURE
Fahrenheit to centigrade: \( ^\circ \text{C} = (^\circ \text{F} - 32) \times \frac{5}{9} \)
Centigrade to Fahrenheit: \( ^\circ \text{F} = (^\circ \text{C} \times \frac{9}{5}) + 32 \)

PRESSURE
1 mm Hg = 1.36 cm H₂O (A pressure of 10 mm Hg = 13.6 cm H₂O.)
1 cm H₂O = 0.73 mm Hg

LENGTH
1 inch (in.) = 2.54 cm
1 cm = 0.394 in.

WEIGHT
1 pound (lb) = 0.454 kg
1 kilogram (kg) = 2.2 lb
1 grain (g) = 60 mg

WORK
1 joule = 1 watt second
1 joule = 0.1 kg \times m
1 joule = 10 cm H₂O \times 1 liter

RESISTANCE
1 hybrid (Wood) unit = 80 dyne \cdot cm \cdot s^{-5}

Useful Renal Formulas and Normal Values

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Formula</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated creatinine clearance</td>
<td>( \frac{140 - \text{age}}{72 \times \text{serum}[\text{Cr}]} \times \text{wt in kg} )</td>
<td>&gt;100 mL/min</td>
</tr>
</tbody>
</table>
Renal failure index (RFI) \[ \frac{\text{Urine}[\text{Na}^+] \times \text{Serum}[\text{Cr}]}{\text{Urine}[\text{Cr}]} \]
- <1 Prerenal
- >1 Intrarenal or Postrenal

Fractional excretion of sodium (FENa) \[ \frac{\text{Urine}[\text{Na}^+] \times \text{Serum}[\text{Cr}]}{(\text{Serum}[\text{Na}^+] \times \text{Urine}[\text{Cr}])} \]
- <1 Prerenal
- >1 Intrarenal
- >4 Postrenal

Anion gap (AG) \[ [\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-]) \]
- 8-12 mEq/L

Calculated osmolality (Osm) \[ 2 \times [\text{Na}^+] + \frac{[\text{glucose}]}{18} + \frac{[\text{BUN}]}{2.8} \]
- 275-295 mOsm/L

Calculated H₂O deficit (liters) \[ 0.6 \times \text{wt in kg} \times (([\text{Na}^+] - 140)/140) \]

Corrected [Ca²⁺] \[ [\text{Ca}^{2+}] \downarrow \text{by } 0.8 \text{ mg/dL} \]
- 8.4-11 mg/dL

Colloid osmotic pressure (COP) \[ 1.4 \times [\text{globulin}]^b + 5.5 \times [\text{albumin}]^b \]
- 24 ± 3 mm Hg

\( ^a \) wt, weight; ↑, increased; ↓, decreased.

\( ^b \) gm/dL, grams per deciliter.

### Useful Circulatory Formulas and Normal Values\(^a\)

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Formula</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (MAP)</td>
<td>((P_{\text{sys}} + 2P_{\text{dia}})/3)</td>
<td>&gt;70 mm Hg</td>
</tr>
<tr>
<td>Physiologic heart rate max (HR(_{\text{max}}))</td>
<td>220 - age</td>
<td>130-200</td>
</tr>
<tr>
<td>Central venous pressure (CVP)</td>
<td>5-12 cm H₂O</td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary artery pressure ((P_{\text{PAP}}))</td>
<td>10-17 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary capillary wedge ((P_{\text{PW}}))</td>
<td>5-12 mm Hg</td>
<td></td>
</tr>
</tbody>
</table>
Cardiac output (CO) \( \text{HR} \times \text{Stroke volume} \) 

Body surface area (BSA) \[ 0.202 \times \text{wt}^{0.425} \times \text{ht}^{0.725} \] 1.5-2.0 m²

Stroke volume (SV) \( \frac{\text{CO}}{\text{HR}} \) >60 mL

Cardiac index (CI) \( \frac{\text{CO}}{\text{BSA}} \) >2.5 L/min/m²

Systemic vascular resistance (SVR) \( \frac{\text{MAP} - \text{CVP}}{80/\text{CO}} \) 900-1,200 dyne·s·cm⁻⁵ (11-15 Wood units)

Pulmonary vascular resistance (PVR) \( \frac{\left( P_{\text{pa}} - P_{\text{wedge}} \right)}{80/\text{CO}} \) 150-250 dyne·s·cm⁻⁵ (2-3 Wood units)

Ejection fraction (EF) \( \frac{\text{SV}}{\text{end-diastolic volume}} \) LV > 60%, RV > 50%

Circulating blood volume approx. 70 mL/kg approx. 5,000 mL

Oxygen delivery \( \text{CO} \times \text{CaO}_2 \) approx. 700 mL O₂/min/m²

\( ^a \text{LV}, \text{left ventricle}; \text{RV}, \text{right ventricle}; \text{wt}, \text{weight}; \text{ht}, \text{height}; P_{\text{pa}}, \text{mean pulmonary artery}; P_{\text{sys}}, \text{systolic pressure}; P_{\text{dia}}, \text{diastolic pressure}; \text{CaO}_2, \text{arterial O}_2 \text{ content.} \)

---

### Useful Respiratory Formulas and Normal Values

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Formula</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume (V₁), resting</td>
<td>5-7 mL/kg pbw(^a)</td>
<td>300-600 ml (body size dependent)</td>
</tr>
<tr>
<td>Vital capacity (VC)</td>
<td></td>
<td>65-70 mL/kg pbw</td>
</tr>
<tr>
<td>Maximal inspiratory pressure (MIP)</td>
<td></td>
<td>&gt;75-100 cm H₂O (neg.)</td>
</tr>
<tr>
<td>Dead space (V₂)</td>
<td>approx. 1/3 V₁</td>
<td>1 mL/pound or 0.45 mL/kg</td>
</tr>
<tr>
<td>Parameter</td>
<td>Formula</td>
<td>Value</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Dead space ratio ($V_D/V_T$)</td>
<td>$(\text{PaCO}<em>2 - P</em>{E\text{CO}_2})/\text{PaCO}_2$</td>
<td>0.25-0.40</td>
</tr>
<tr>
<td>Minute ventilation ($V_E$), resting</td>
<td></td>
<td>5-10 L/min</td>
</tr>
<tr>
<td>Maximal ventilatory volume (MVV)</td>
<td>approx. $35 \times \text{FEV}_1$</td>
<td>70-140 L/min</td>
</tr>
<tr>
<td>Peak flow</td>
<td>(height, age, gender dependent)</td>
<td>$&gt;$7 L/s or $&gt;$425 L/min</td>
</tr>
<tr>
<td>Dynamic characteristic</td>
<td>$V_T/(P_{aw} - \text{PEEP})$</td>
<td>Flow dependent</td>
</tr>
<tr>
<td>Static respiratory system compliance ($C_{stat}$)</td>
<td>$V_T/(P_{plat} - \text{PEEP})$</td>
<td>80 mL/cm H$_2$O</td>
</tr>
<tr>
<td>Resistance to airflow ($R_L$)</td>
<td>$(P_{\text{dyn}} - P_{\text{stat}})/\text{flow}$</td>
<td>$&lt;$4 cm H$_2$O/L/s</td>
</tr>
<tr>
<td>Alveolar partial pressure of O$_2$ (PAO$_2$)</td>
<td>$(P_b - P_{\text{H}_2\text{O}}) \times \text{FiO}_2 - \text{(PaCO}_2)/0.8$</td>
<td>$&gt;$100 mm Hg</td>
</tr>
<tr>
<td>Alveolar-arterial difference (A-aDO$_2$)</td>
<td>PAO$_2$ - PaO$_2$</td>
<td>$&lt;$10 mm Hg @ FiO$_2$ = 0.21</td>
</tr>
<tr>
<td>Arterial PaO$_2$/FiO$_2$ ratio (P/F)</td>
<td>PaO$_2$/FiO$_2$</td>
<td>$&gt;$425 (age dependent)</td>
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<tr>
<td>Arterial/alveolar PO$_2$ ratio (a/A)</td>
<td>PaO$_2$/PAO$_2$</td>
<td>$&gt;$0.9</td>
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<td>Arterial O$_2$ tension (PaO$_2$)</td>
<td>approx. 100 - (age/3)</td>
<td>80-95 mm Hg</td>
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<tr>
<td>Arterial O$_2$ saturation (SaO$_2$)</td>
<td>SaO$_2$ &gt;90%</td>
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<tr>
<td>Arterial CO$_2$ tension (PaCO$_2$)</td>
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<td>37-43 mm Hg</td>
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<tr>
<td>Mixed venous O$_2$ tension (P[\text{v with bar above}]O$_2$)</td>
<td>approx. 35-40 mm Hg</td>
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<tr>
<td>Mixed venous O$_2$ saturation (S[\text{v with bar above}]O$_2$)</td>
<td></td>
<td>$&gt;$70%</td>
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<tr>
<td>Mixed venous CO$_2$ tension (P[\text{v with bar above}]CO$_2$)</td>
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<td>approx. 45 mm Hg</td>
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</table>
Arterial O\textsubscript{2} content (CaO\textsubscript{2}) \( (\text{Hgb} \times 1.34)\text{SaO}_2 + (\text{PaO}_2 \times 0.003) \) approx. 20 mL/dL

Venous O\textsubscript{2} content (C\{v with bar above\}O\textsubscript{2}) \( (\text{Hgb} \times 1.34)\text{S\{v with bar above\}O}_2 + (\text{P\{v with bar above\}O}_2 \times 0.003) \) approx. 15 mL/dL

Oxygen consumption (VO\textsubscript{2}) \( \text{CO} \times (\text{CaO}_2 - \text{C\{v with bar above\}O}_2) \) approx. 250 mL/min

Extraction ratio \( (\text{CaO}_2 - \text{C\{v with bar above\}O}_2)/\text{CaO}_2 \) approx. 0.25-0.30

Pulmonary capillary O\textsubscript{2} content (CcO\textsubscript{2}) \( (\text{Hgb} \times 1.34) + (\text{PAO}_2 \times 0.003) \) approx. 20 mL/dL

Shunt fraction (venous admixture) \% \( ([Q \text{ with dot above}]_s/[Q \text{ with dot above}]_t)(\text{CcO}_2 - \text{CaO}_2)/(\text{CcO}_2 - \text{C\{v with bar above\}O}_2) \times 100 \) <5%

Arteriovenous O\textsubscript{2} content difference \( \text{CaO}_2 - \text{C\{v with bar above\}O}_2 \) approx. 5 mL/dL

\textsuperscript{a}Pbw, lean body weight; \textsubscript{PE}CO\textsubscript{2}, mixed expired PCO\textsubscript{2}; \textsubscript{PB}, barometric pressure, in mm Hg; \textsubscript{P\{w\}O}, water vapor pressure at body temperature.

### Content of Common Intravenous Fluids

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<tr>
<th>Type</th>
<th>Na\textsuperscript{+}</th>
<th>Cl\textsuperscript{−}</th>
<th>K\textsuperscript{+}</th>
<th>Ca\textsuperscript{2+}</th>
<th>Lactate</th>
<th>HCO\textsubscript{3}⁻</th>
<th>mOsm/L</th>
<th>kcal/L</th>
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<th>°F</th>
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<th>pH</th>
<th>PCO₂ (%)</th>
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